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THE MECHANISM OF ADJUSTMENT OF THE CIRCULATION IN HYPERTHYROIDISM (THYROTOXICOSIS)*

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WASHINGTON, D. C.

CERTAIN facts have been learned about the circulation in hyperthyroidism, from both clinical and laboratory investigations, which allow one to speculate intelligently upon the probable mechanism of adjustment of the circulation in that condition. These facts will be briefly given.

Cardiac overactivity is one of the outstanding evidences of hyperthyroidism. It is indicated by both subjective and objective symptoms. The latter are mainly tachycardia, loud heart sounds, enlargement of the area of cardiac dullness and increased pulse pressure.

That there is an increase in the minute-volume output of the heart and a greater velocity of blood flow through the lungs and the tissues has been amply demonstrated both in patients and in animals by competent workers^{2, 3, 4, 7, 9, 14, 16, 20, 21, 22, 25} using different experimental methods. The general conclusion has been that there is a fairly close correlation between the oxygen consumption (basal metabolic rate) and the output of the heart in hyperthyroidism. Several workers have noted that the minute-volume output of the heart, however, increased relatively more than the oxygen consumption, so that the oxygen needs of the tissues are supplied without diminishing the oxygen tension of the mixed venous blood. Plummer and Boothby²² showed that for a given amount of work by patients with hyperthyroidism there is a disproportionate rise in the metabolic rate which requires a similar disproportionate rise in ventilation and in blood-flow. In dogs fed thyroid substance Blalock and Harrison² found that the cardiac output increased as the oxygen consumption increased, but that the rate of increase in cardiac output was at first less than that of the oxygen consumption, although later

*From the Georgetown University School of Medicine.

the output increased rapidly and showed a greater relative elevation than the metabolic rate. These facts all indicate that while the demands of the tissues for more oxygen are met by a greater blood flow, the adjustment is not as accurate as it is in the corresponding physiological state, muscular exercise.

The increase in the pulse pressure in hyperthyroidism is a constant phenomenon.^{10, 12, 28} It is effected by a moderate increase in the systolic pressure without much alteration of the diastolic pressure. A relationship between the pulse pressure and the basal metabolic rate has been noted,^{3, 6, 29} the pulse pressure being greater the higher the basal metabolic rate. The increased pulse pressure, the visible throbbing of the vessels generally, and the frequently observed capillary pulsation are all indicative of general vascular relaxation, which is a necessary concomitant of increased blood flow.

There is an actual increase in the circulating blood volume in hyperthyroidism, as shown by Wislicki³⁰ and by Chang.⁵ This increase may be as great as 30 per cent, and involves the plasma and cellular elements proportionally. It may be due to contraction of the spleen, as in exercise, but there are probably also other factors.

Since tachycardia is such an outstanding and constant feature of hyperthyroidism, it has received considerable attention. It is present even during sleep, and the basal pulse rate when computed with the pulse pressure has been found to give a fairly accurate indication of the degree of elevation of the basal metabolic rate.^{3, 13, 19, 24, 26} The cause of the tachycardia has until recently been thought to be a stimulation of the sympathetic nerves, an increased production of adrenalin or a toxic influence on the myocardium. Several groups of investigators have independently proved that these theories are wrong.

J. K. Lewis and McEachern¹⁵ published the results of experiments with rabbits' hearts which showed that the isolated hearts of thyroxinized animals persist beating at an accelerated rate. Priestly, Markowitz and Mann²⁸ also found that the hearts of thyroxinized rabbits when perfused beat faster than normals.* In an ingenious experiment they demonstrated that the heart of a pup which had been anastomosed to the vessels of the neck of a large dog beat much faster when the large dog was thyroxinized. In a large series of rabbits made acutely hyperthyroid by intravenous injection of thyroxin I³¹ found uniformly that the isolated perfused hearts beat much faster for many hours than the hearts of rabbits not thyroxinized. The average rate of the perfused hearts of normal rabbits was 140 per minute and that of the acutely thyroxinized rabbits was 193 per minute, an increase of 38 per cent. The effect of one injection of thyroxin became manifest by the increased heart rate after a latent period of two days and persisted for two weeks.

*The few exceptions were probably due to the fact that the latent period of action of thyroxin had not been recognized.

I noted in these experiments that the hearts of the thyroxinized rabbits were more subject to attacks of arrhythmia and seemed to beat more vigorously than normal. After excision of the sino-auricular node of the perfused hearts of thyroxinized rabbits the heart rate was still greatly increased when compared with controls, and after anriculo-ventricular dissociation was produced by crushing the bundle of His, the ventricles usually continued to beat at an accelerated rate. McIntyre¹⁸ has laboriously completely denervated the hearts of dogs and has found that when the animals were made hyperthyroid the heart beat faster to the same degree as in control dogs. These experiments all showed that thyroxin exerts its effect either upon the muscle fibers or upon the nerve endings in the myocardium. It remained for Cecile Markowitz¹⁷ to show conclusively that thyroxin acts directly upon the muscle fibers. A study was made of the action of thyroxin on tissue cultures of pulsating fragments of heart muscle removed from chick embryos before the appearance of nerve elements in the heart. A progressively greater increase in rate of pulsation occurred, ending in some cases in fibrillation and paralysis.

Some experimental work has been done to compare the survival period of isolated perfused hearts of thyroxinized rabbits with that of hearts of non-thyroxinized rabbits. I studied in this way the hearts of both acutely thyroxinized rabbits and of rabbits kept hyperthyroid for a long period of time. These hearts continued to beat as long as, and possibly better on the average than normal hearts.

With these facts before us we may speculate upon the mechanism by which the circulatory adjustments in hyperthyroidism are made. In order to arrive at a satisfactory conception of this problem it is necessary to review the adjustment of the circulation in the most nearly corresponding physiological state. This state is muscular exercise, since the patient with hyperthyroidism has a circulation rate at rest which is the same as that of an individual undertaking moderate physical exertion.

Bainbridge¹ has written a classical treatise on the physiology of muscular exercise, and this, together with the monograph of Wiggers²⁸ on the pressure pulses in the cardiovascular system, comprises the main source of information for the following brief account of the circulatory adjustments in exercise.

The oxygen needs of the body per minute during exercise are increased in proportion to the amount of external work performed. This correlation is accomplished by a carefully regulated series of adjustments. In the first place an increase in pulmonary ventilation, which determines largely the oxygen supply of the body, is brought about by a rise in the hydrogen ion concentration of the blood and a greater sensitiveness of the respiratory center; the latter is probably due to the effect upon this center of impulses from the higher centers of the brain flowing out concomitantly with the passage of impulses from the cerebral cortex to

the skeletal muscles. A more rapid circulation rate closely correlated with the degree of increase in pulmonary ventilation is necessary in order that the needs of the tissues for more oxygen may be met. The law of the heart (Starling) states that the ventricles can eject all of the blood which enters them in diastole, and that they do so with the greatest force possible at the time. In exercise more blood is returned to the heart than during rest because of the mechanical squeezing of blood out of the capillaries of the voluntary muscles by the increased activity of the muscles, and also because of the accelerated and augmented respiratory movements, particularly of the diaphragm. In response to a greater venous inflow the heart can increase its output per minute either by a larger output per beat or by acceleration of the pulse rate. The influence of the latter upon the output of the heart per minute is determined by the rate at which the heart fills during diastole. If the venous inflow is adequate, i. e., if it is so rapid that the heart fills almost completely early in diastole, acceleration of the pulse only slightly diminishes the output per beat but greatly increases its output per minute. Thick-walled, well nourished ventricles (such as in athletes) increase their output more by a greater volume per beat than by acceleration of rate. The initial acceleration of the pulse rate at or just before the beginning of exercise is due to the passage of impulses from the higher centers to the vagus center whereby its tone is lessened and to the accelerator nerves whereby their tone is increased. The persistent acceleration of the pulse throughout the period of exercise depends, partly on a continuance of the outflow of impulses from the cerebral cortex to the vagus and accelerator centers, partly on the influence upon the vagus center of the rise in temperature of the body, and partly on the greater diastolic distension of the auricles which reflexly lessens the tone of the vagus center (Bainbridge's reflex). The effectiveness of the larger output in increasing the blood supply to the active muscles, the heart and the brain during exercise is greatly enhanced by constriction of the splanchnic vessels and by dilatation of the vessels of the muscles and heart. The former is brought about primarily and chiefly by the outflow of impulses from the higher centers to the vasomotor center; the latter by the reduction of tone of the arterioles and capillaries directly by the action of acid and other metabolites in the muscles and possibly by the effect of an addition of small amounts of adrenalin to the circulation. The rise of arterial pressure is the resultant of (1) the increased output of the heart, (2) the constriction of the splanchnic vessels, and (3) the dilatation of the vessels in the muscles and skin.

Hyperthyroidism differs from muscular exercise in two main features: (1) the absence of the outflow of impulses from the cerebral cortex to the muscles and the medullary centers, and (2) the absence of increased activity of the muscles, which is perhaps the most important factor in the return of blood to the heart. While an increase in rate and ampli-

tude of respiration is not a prominent feature in hyperthyroidism, it exists, as was first shown by Hofbauer,¹¹ and is probably due to the effect of an increase in hydrogen ion concentration of the blood upon the respiratory center. To a certain extent this increased respiratory activity aids in the return of blood to the heart. The increased metabolism of the tissues undoubtedly accounts mainly for the general vascular relaxation in the same way as in exercise, and this relaxation is of importance in the acceleration of the return of blood to the heart. The increase in blood volume augments the effect of vascular relaxation and allows the filling of the heart to be adequate in spite of the larger size of the stream-bed.

The main differences between exercise and hyperthyroidism are concerned, therefore, with the mechanism of increase in the cardiac output and of the acceleration of the pulse rate. It would appear from the experimental work reported that the two factors largely responsible for this increase in the minute-volume output of the heart in hyperthyroidism are the acceleration of the pulse rate and the increased vigor of the heart beat. The former has been shown adequately to be due entirely to the effect of an excessive amount of thyroxin in the heart muscle itself and not to the causes of acceleration of the pulse rate which exist in exercise. The increased vigor of beat is indicated by the loudness of the heart sounds, the increased systolic blood pressure in spite of general vascular relaxation and the apparent exaggeration of force of the beat in perfused hearts. A study of the cardiac dynamics of hyperthyroid hearts of animals would be of great value in accurately establishing this point. It is probable that the hyperthyroid heart more completely empties itself early in systole and fills rapidly early in diastole, so that the tachycardia is itself responsible for a great increase in the minute-volume output of the heart. Since the acceleration of the heart rate and the increased vigor of heartbeat are due entirely to the effect of thyroxin upon the heart muscle, it is, therefore, entirely a coincidence that there exists in hyperthyroidism an increased blood flow and velocity of the circulation. Were it not for this fact patients with hyperthyroidism would soon suffer from relative tissue anoxemia and the metabolic rate be decreased. This fact also accounts for the inexact correlation of the rate of oxygen consumption and the increased blood flow.

The ample oxygen supply of the heart itself and the reduction of resistance to blood flow through the tissues probably explain why congestive heart failure is so infrequent until the later decades of life in spite of the increase in amount of work done by the heart. The lack of any great degree of hypertrophy of the heart in hyperthyroidism is probably due to the fact that the peripheral stream-bed is wide open, so that the increased effort of the heart is expended largely upon the increased frequency of the pulse rate and not in overcoming mechanical obstruction to the flow of blood.

Investigators in the field of hyperthyroidism have uniformly passed over the increased rate of circulation by stating that it is due to the greater demands of the tissues for oxygen. To quote a few, Du Bois⁸ stated that "Part of the increase in pulse rate is also due directly to the increased metabolism which necessitates a greater blood flow;" Willius and Boothby²⁸ said that "In view of the constant elevation in the basal metabolic rate in exophthalmic goiter and in adenomatous goiter with hyperthyroidism, it is obvious that there must be an increase in the rate of circulation to meet the increased demand of the tissues for the transportation of electrolytes;" and Blumgart, Gargill and Gilligan³ asserted that "The increased velocity of blood flow in thyrotoxicosis probably occurs to meet the demands of the elevated metabolic rate and not as a result of a toxic effect on the heart." Now it may safely be stated that it is only because of the effect of an excessive amount of thyroxin in the myocardium itself that these "demands" are met.

SUMMARY AND CONCLUSIONS

The facts known regarding the alterations of the circulation in hyperthyroidism have been stated. From these it appears that the increase in the rate of the circulation is a fortuitous rather than a physiological adjustment. It is due mainly to the increase of thyroxin in the myocardium which causes the heart to beat more rapidly and more vigorously. Associated with this are a general vascular relaxation brought about by the local action of metabolites on the arterioles and capillaries, and an increase in the circulating blood volume, due mainly perhaps to contraction of the spleen. There is probably also an increase in rate and depth of respiration, the result of the effect of an increased hydrogen ion concentration on the respiratory center. These factors aid in the more rapid return of blood to the heart.

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(For discussion, see page 143.)

CARDIAC HISTOPATHOLOGY IN THYROID DISEASE. PRELIMINARY REPORT*

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THE cardiac histopathology of thyroid disease has been studied by many observers and very many conflicting reports have been made. Grant¹ found dilated and hypertrophied hearts with little evidence of myocardial degeneration. Many showed a mild myocardial scarring, round-cell infiltration or fatty degeneration, but not sufficient to account for the great disturbance in cardiac function. In some instances there was an acute myocardial necrosis, but this was unusual.

Wilson² described the myocardium in eighteen cases of hyperthyroidism as showing swollen fibers with indistinct striations and well marked lipoid changes. Only five patients were under forty years of age. In patients with long-continued pronounced hyperthyroidism, the myocardium shows more advanced fatty changes than are present in the myocardium of individuals of the same age without hyperthyroidism.

In eighteen cases of Basedow's disease and in nine cases of colloid struma with Basedow's disease, Fahr³ found in the myocardium, fibroblastic proliferation and scars. In cases of colloid struma with cardiac disturbances he described small round cell infiltrations between the muscle fibers and around the small vessels. He regarded these changes as true inflammation. Beyond the infiltration was a slight degenerative fatty infiltration. He stressed the differences in intensity of the changes.

Ceelen⁴ found sharply localized necroses with areas of fibroblastic reaction in hearts of Basedow's disease.

No proof of Fahr's findings of infiltrations and true myocarditis could be found by Baust.⁵ He recognized only a slight increase in lymphocytes and fibroblasts, but no degenerative changes with fibrosis and scars.

Kerr and Rusk,⁶ in a case of hyperthyroidism, described in the myocardium occasional moderate separation of the fibers by edema. One small focus of fibrosis without any evidence of exudative cells in relation to it was seen. In one section a marked perivascular lymphocytic infiltration was seen. No evidence of focal necrosis of the myocardium was observed.

Loos⁷ described hypertrophy and dilatation of the heart with microscopical findings of fatty infiltration and lipofuscin formation, areas of round cell infiltration with necrosis, and scars in the muscle. These changes he believed due to toxin from the thyroid and mentioned the re-

*From the Department of Pathology, University of Michigan.

semblance to the multiple necroses in hearts damaged by carbon monoxide and diphtheria toxin.

Askanazy⁸ described brown atrophy, degenerative fatty infiltration and an interstitial myocarditis with Basedow's disease; and in eight cases of Basedow's disease, Matti⁹ found six with foci of fatty infiltration and one with destruction of muscle fibers, without inflammatory infiltrations. Pettavel¹⁰ reported constant scattered and diffuse fatty infiltration. Simonds¹¹ in eight cases found only one with fibrous nodules in the muscle. This case was also excluded because of synechia of the pericardium, indicating a complication. Takane¹² had three cases with inflammatory round cell infiltrates in the heart in association with thyroid disease. Hashimoto¹³ examined two hearts from exophthalmic goiter patients and found lymphocytic infiltrations between the muscle fibers or around the blood vessels.

Chesky¹⁴ wrote that, while a few cases dying with hyperthyroidism show small scars, fatty degeneration and interstitial and perivascular round cell infiltration, similar lesions are found as a part of the degenerative changes of age in patients without goiter.

The conclusion of White¹⁵ was that there is no constant cardiovascular lesion in thyrotoxicosis. Enlargement and hypertrophy of the fibers is present in some chronic cases, but it is difficult to exclude factors of hypertension and coronary disease. In a few cases necrosis of the myocardium has been found, but this has not been confirmed as a thyroid effect. The heart weight is generally increased only slightly.

Rautmann¹⁶ found hypertrophy and dilatation but no inflammatory or degenerative changes, even in the most severe Basedow cases. In his very complete work he said that the anatomical changes in Basedow's disease are either an hypertrophy-hyperplasia or atrophy-hypoplasia. The hypertrophy and hyperplasia are chiefly met with in the thyroid, thymus, general lymphoid tissue and in heart muscle. The atrophy and hypoplastic changes occur in the adrenals.

METHOD OF INVESTIGATION

In the series of 4200 autopsies at the University of Michigan, there have been 43 instances of exophthalmic goiter and 90 of adenomatous goiter. This material, after a certain amount of selection, forms the basis for the present study. From these two groups there were deleted all those for which permission for a reasonably complete autopsy was not given and also those cases showing any evidence of syphilis, rheumatic fever, infective endocarditis or severe coronary atherosclerosis, on the basis that myocardial changes are exceedingly common in these diseases. As far as possible, known causes of frequent extensive myocardial changes were thus eliminated. Each individual of this greatly shortened autopsy list was then matched as closely as possible with another of the same age, sex and major cause of death, but without thyroid

disease. Thus a definite control series was established, differing from the first only in the factor of thyroid disease. If any distinctive myocardial lesion appears as the result of thyroid disease, it should be evident from the comparison of the two series. In this manner two groups of cases were set up; one with exophthalmic goiters and the other with adenomatous goiters, upon all of which complete autopsies had been performed.

A review of the gross autopsy findings was followed by a microscopical study of the hearts and thyroids from all cases with reference to specific deviations from the normal. In the gross examination, note was made of the total weight of the heart and the thickness of the ventricles. From each heart, at least four and in some cases eight or ten blocks were examined; these included both ventricles and auricles together with all valvular orifices. Where additional sections were needed, as many as seemed necessary to give a complete microscopic representation were prepared.

In reviewing the heart and thyroid material, no attention was paid to previous diagnoses, many of which were separated by thirty-five years in time. Instead, the entire series was evaluated objectively and with as uniform an application of the various criteria as could be employed.

The microscopic examination involved the tabulation of the following 13 items with the indicated connotations:

1. *Atrophy of Myocardium*.—A positive judgment of atrophy was based upon the finding of muscle fibers smaller in size than is normal for the particular age, with oftentimes increased lipoidal pigment about the nuclei and an apparent or relative increase of stroma cells due to condensation of the connective tissue.

2. *Hypertrophy of Myocardium*.—The presence of enlarged fibers with large and hyperchromatic nuclei was taken as the evidence of hypertrophy.

3. *Hypoplasia of Myocardium*.—Fibers of small size but without increase in pigment and without any attendant increase in stroma were considered hypoplastic rather than atrophic.

4. *Zenker's Necrosis*.—This is the classical intracellular coagulation necrosis denoted by palely staining fibers with loss of nuclear differentiation.

5. *Fragmentation of Fibers*.—This phenomenon, probably in itself entirely post-mortem, may indicate a previous change in physical state of the muscle fibers.

6. *Edema*.—In heart muscle, edema is indicated by the swelling and separation by albuminous fluid of the connective tissue cells and fibers.

7. *Cloudy Swelling*.—A swelling of the fiber associated with slight loss in stainability of the nucleus and cytoplasm, where the section generally does not indicate such change to be post-mortem, has been construed to be cloudy swelling.

8. *Fatty Infiltration*.—This is an excess of adipose tissue beneath the epicardium with interdigitation of the outer muscle fibers and fat cells.

9. *Degenerative Fatty Infiltration*.—Unlike the foregoing, degenerative fatty infiltration is an accumulation of fat in many small vacuoles in the cytoplasm of muscle fibers and is associated with degenerative nuclear changes. This is usually most marked immediately beneath the endocardium.

10. *Sclerosis of Small Coronary Branches*.—Cases with important obliterative changes of the large coronary vessels were eliminated from the series. Examination of the small branches was done to assist in making an etiological judgment concerning any areas of fibrosis.

11. *Fibrosis of Myocardium*.—The amount of connective tissue, location and correlation with active inflammation was observed.

12. *Endocardial Sclerosis*.—The positions of these areas as well as the severity of the process were considered in relation to the existence and position of fibroid areas.

13. *Cellular Infiltrations*.—The extent, together with the severity and character of these, was noted.

EXOPHTHALMIC GOITER

The arithmetical mean of the weights of the hearts of both the exophthalmic goiter series and its controls are given in Table I, together with the calculated probable errors of the means and the average measurements of the ventricles. It is to be noted that while there is a difference of 60 grams in the means of cardiac weights, the variability in both series is so great that a difference of the magnitude found may be expected as an error of random sampling. The same conclusion is reached when the

TABLE I

	EXOPHTHALMIC GOITER SERIES	CONTROL SERIES
Weight of Heart, Mean	393 \pm 46 grams	323 \pm 75 grams
Left Ventricle, Mean	17.2 \pm 2.0 mm.	19.0 \pm 2.5 mm.
Right Ventricle, Mean	5.6 \pm 1.4 mm.	6.5 \pm 1.2 mm.

weight of each control heart is subtracted from its companion and the differences treated statistically, the mean preponderance of the exophthalmic goiter hearts over those of the control series being 47 ± 94 grams, there being several cases in which the weight of the control hearts greatly exceeded the ones with which they were paired.

The results of the microscopic examination are given in Table II where it is at once evident that while there are several pathological features

TABLE II

EXOPHTHALMIC GOITER	GOITER CASES		CONTROLS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total cases used in microscopic examination	35	100	35	100
Atrophy of myocardium	3	8.6	12	34.3
Hypertrophy of myocardium	23	65.7	21	60.0
Hypoplasia of myocardium	21	60.0	7	20.0
Zenker's necrosis	8	22.8	4	11.4
Fragmentation of fibers	5	14.3	7	20.0
Edema	11	31.4	7	20.0
Cloudy swelling	25	71.5	22	62.8
Fatty infiltration	15	42.8	17	48.6
Fatty degenerative infiltration	24	68.6	22	62.8
Sclerosis of small coronary branches	16	45.7	16	45.7
Fibrosis of myocardium	28	80.0	18	51.5
Endocardial sclerosis	31	88.6	18	51.5
Cellular infiltrations	11	31.4	6	17.1

having a high incidence in the exophthalmic goiter series, there are only four items which are at all impressive in comparison with similar findings in the controls. These are: hypoplasia of myocardium, fibrosis of myocardium, endocardial sclerosis and cellular infiltrations. The evidence upon which the conclusion of hypoplasia was based was found only in the right ventricle and, in general, was not a very outstanding feature.

Of the exophthalmic goiter hearts, 80 per cent showed patches of fibrosis which for the most part were associated with endocardial sclerosis and were found chiefly in the left ventricular wall and in the papillary muscles. These changes had no definite vascular associations although frequently they would be adjacent to small vessels. The lesions



Fig. 1.—A-249-AJ. Active inflammatory focus with fibrosis beneath endocardium. $\times 95$.

were usually small and for the most part had not been seen in the gross examination. In contour, they were irregular, the peripheral strands interdigitating with the surrounding muscle fibers, but very few of them showed any evidence of survival of muscle fibers within the area of fibrosis. Concerning the character of the lesions, no specific features could be determined save that they were not related to vascular obliteration. In view of the preliminary exclusion of such causes from the series, it can be positively stated that these lesions were not due to syphilis, rheumatic fever or coronary disease.

Of the eleven cases of the exophthalmic goiter series showing cellular infiltrations, six showed only subepicardial foci of wandering cells, this being also the localization of infiltrations shown by the six controls. Of the remaining five exophthalmic goiter cases, one showed such an active and unusual myocarditis that it merits more detailed consideration.

This patient, a woman 41 years of age, was admitted to the University Hospital in stupor, and the meager history was obtained from relatives. She had had definite goiter with exophthalmos for ten years with a marked increase of symptoms three weeks before entering the hospital and with vomiting for the last week of that pe-

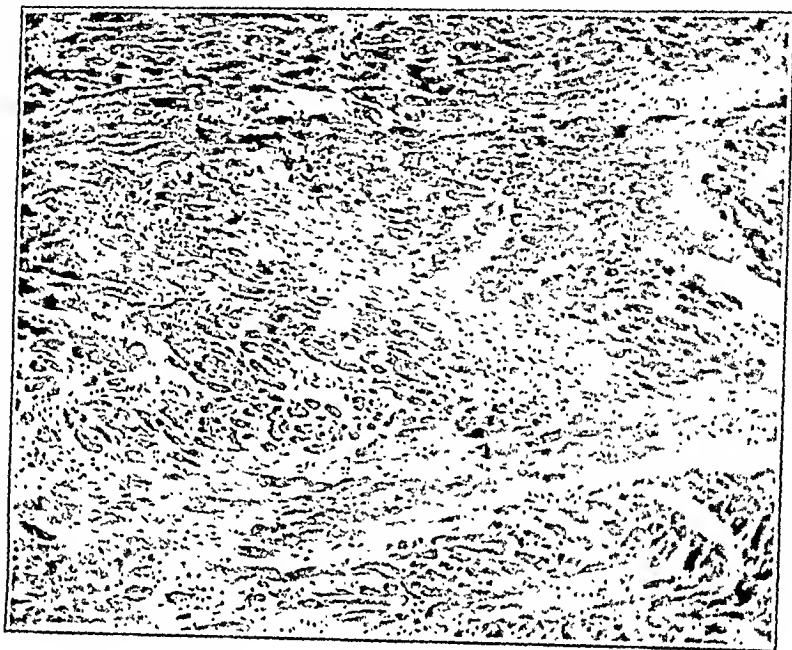


Fig. 2.—A-249-AJ. Small inflammatory focus deep in myocardium. $\times 95$.

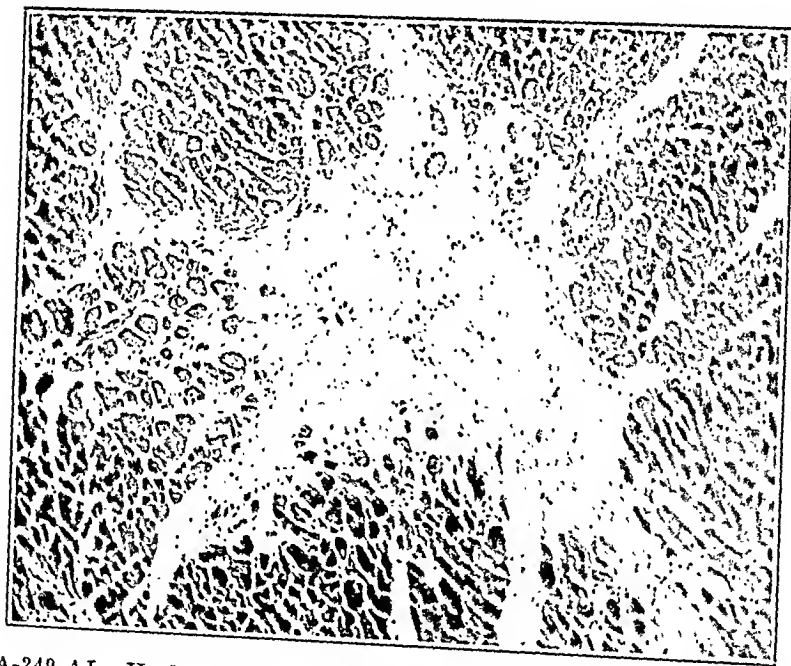


Fig. 3.—A-249-AJ. Healed lesion. Hyaline connective tissue. No active infiltration. $\times 95$.

riod. On examination there was definite cardiac enlargement, a systolic murmur at the apex, a pulse of 110, and a blood pressure of 160/75 mm. Electrocardiogram showed a sinus tachycardia with inverted T-waves in leads I and II. A diagnosis of thyroid crisis was made, intensive lugolization and digitalization were started and

x-ray administered to the thyroid. The condition grew worse and the patient died six days after entering the hospital.

At autopsy the heart was found to weigh 400 grams and measured $11 \times 11 \times 7.5$ cm. The left ventricle was 25 mm. in thickness; the right ventricle measured 11 mm.

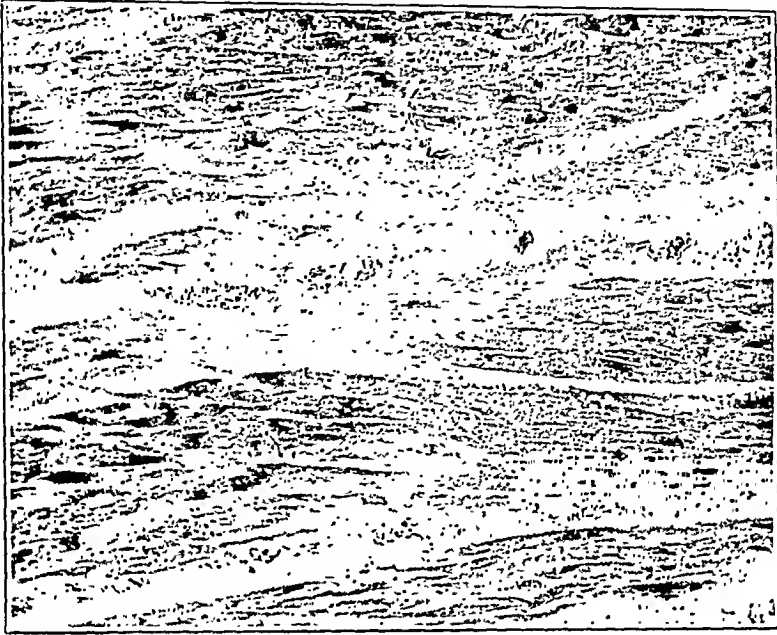


Fig. 4.—A-125-Z. Small area of fibrosis. No active inflammation. $\times 95$.



Fig. 5.—A-125-Z. Extensive fibrosis with survival of muscle fibers. $\times 95$.

Both ventricles were dilated. Microscopically, a moderate hypertrophy of the muscle fibers and a moderate atherosclerosis of the larger coronary arteries were found. Most striking, however, were the many focal lesions occurring throughout the myocardium, even that of the auricles. These were strictly nonpurulent and could be

found in all stages from focal necroses of the muscle fibers with lymphocyte and plasma-cell infiltrations to old and somewhat hyaline patches of fibrosis. The lesion was essentially a fibroblastic proliferation in response to focal necrosis rather than a diffuse interstitial fibrosing process. Various stages in the evolution of these fibroid areas are shown in Figs. 1 to 3.

In four other hearts, cellular infiltrations associated with patchy fibrosis were found, but in none of these were early lesions seen and the wandering cells were relatively sparse. In general, the fibroid regions resembled the healed lesions of the case showing active myocarditis and likewise there was no obvious explanation of their presence. Typical fibroses are shown in Figs. 4 to 6.

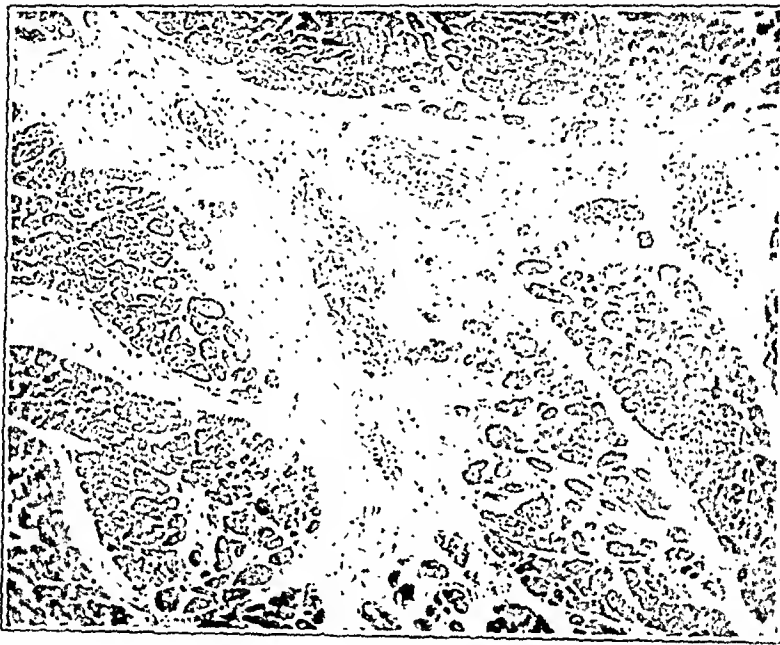


Fig. 6.—A-126-AE. Old perivascular fibrosis extending into myocardium. $\times 95$.

The one case of active myocarditis agrees with those previously described by Fahr, but in this series, unless the numerous fibroses are assumed to be healed focal lesions of that variety, it is not as frequently occurring as Fahr found to be the case in those he studied. It is a reasonable explanation that the numerous fibroid foci are actually the end result of a distinctive myocarditis, but there is no positive proof of this.

With respect to the other pathological changes in the hearts of the exophthalmic goiter series, the incidence of necrobiotic changes such as cloudy swelling and degenerative fatty infiltration is high, but the control series shows correspondingly high values for these items. This is undoubtedly due to the circumstances attending death, and further elucidation of this point is given in Table III where a tabulation of the immediate causes of death shows 21 of the 35 cases to have died of severe infections in which such retrogressive phenomena are the rule.

TABLE III
EXOPHTHALMIC GOITER

19 Males, average age at death	43.6 years
21 Females, average age at death	41.5 years
40 Cases, average age at death	42.5 years
Immediate Causes of Death:	35 cases
Exophthalmic goiter only	2 cases
Cardiac insufficiency	9 cases
Pneumonia	17 cases
Other infections	4 cases
Lymphatic leucemia	1 case
Cerebral hemorrhage	1 case
Asphyxia	1 case
Average duration	3.4 years
Auricular fibrillation	15 cases
Average basal metabolic rate	+48%
Maximum basal metabolic rate	+90%
Minimum basal metabolic rate	+14%

ADENOMATOUS GOITER

After pursuing the same eliminations as in the exophthalmic goiter series, 55 complete autopsies remained showing adenomatous goiters and no evidence of syphilis, rheumatic fever, infective endocarditis or advanced atherosclerosis of the larger coronary arteries. For each of these a control was selected following the same procedure as in the exophthalmic goiter study. The same tabulation of microscopic findings was employed, and the results are given in Table IV. From the data, it appears that no significant difference between the two series existed save in respect to cellular infiltrations. However, in both series, these in-

TABLE IV
ADENOMATOUS GOITER

	GOITER CASES		CONTROLS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total cases used in microscopic examination	55	100	55	100
Atrophy of myocardium	18	33	14	26
Hypertrophy of myocardium	42	76	42	76
Hypoplasia of myocardium	12	22	9	16
Zenker's necrosis	0	0	2	4
Fragmentation of fibers	8	15	8	15
Edema	21	38	16	29
Cloudy swelling	37	67	37	67
Subepicardial fatty infiltration	34	62	42	76
Fatty degenerative infiltration	49	89	50	91
Sclerosis of small coronary branches	22	40	18	33
Fibrosis of myocardium	35	64	40	73
Endocardial sclerosis	39	71	42	76
Cellular infiltrations	17	31	8	15

filtrations were nearly all subepicardial in location; and considering the fact that two-thirds of the adenomatous goiter individuals died of severe infections such as pneumonia and purulent peritonitis, this difference is also probably meaningless. The very high incidence of 89 per cent for degenerative fatty infiltration is in accordance with the reported high figure for that change in this disease, but this is at once discounted by finding it in 91 per cent of the controls.

As far as this evidence goes, we are thus forced to the conclusion that no definitely demonstrable cardiac lesion occurs as the result of adenomatous goiter. All of the changes previously described in such cases can be verified in this series, but when rigidly controlled, it is found that such changes are due to the concomitant conditions of illness rather than to the presence of the thyroid disease.

SUMMARY AND CONCLUSIONS

1. A morphological study of the hearts of 35 patients with exophthalmic goiter showed, with but few exceptions, no gross or microscopical pathological changes not equally represented in a carefully matched control series.

2. The exceptions found were (1) a relatively higher incidence of myocardial fibrosis, endocardial sclerosis, and cellular infiltrations in the series with exophthalmic goiter and (2) one case in the series of 35 which showed an active focal myocarditis for which no etiological factor could be ascertained other than the hyperthyroid state.

3. Twenty-eight, or 80 per cent of the exophthalmic series showed areas of myocardial fibrosis, as compared with 51.5 per cent of the control series. It is impossible to determine to what extent, if any, such areas of fibrosis may be the result of an active myocarditis of the type found in the single case.

4. The hearts of 55 cases of adenomatous (nodular) goiter failed to show any significant difference in the incidence of pathological changes as compared to a matched nongoitrous control series.

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(For discussion, see page 143.)

A STUDY OF THE HEART IN HYPERTHYROIDISM*

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WHILE the opinion commonly held is that the cardiac phenomena in hyperthyroidism are due to a specific toxin produced as a result of the disease and acting specifically on the myocardium, yet those who have had occasion to study the literature dealing with this question will have been impressed with the lack of unanimity, indeed the frank contradictions, which characterize the problem. The concept of structural change as a basis for the cardiac phenomena is in reality founded upon a very small number of reliable clinical reports or experimental protocols. Furthermore, great stress should be laid on the absence of any satisfactory control series of macroscopic and microscopic observations on "presumably" normal hearts in human beings and animals. The literature in question has been carefully studied and reviewed up to the end of 1930 by the present authors in previous papers, to which reference may be had.^{1, 2} It may be stated in brief that in the majority of instances, apart from hypertrophy, either no change was found or else the changes did not exceed those which the present authors have shown to occur in a series of "normal" hearts. In a small number of cases, however, there have been described quite extensive diffuse or local lesions in the myocardium, which have been considered specific. This brief review of the literature serves whether it be applied to papers dealing with human autopsy material or to those discussing the results of experimental observations on rabbits, guinea pigs, rats, etc., after being fed or injected with different preparations of the thyroid gland. Papers appearing since 1930 have, with one exception,³ agreed on the absence of any specific myocardial lesion.

It is pertinent to turn for a moment from human and experimental pathology and to examine the clinical picture of the hyperthyroid patient with cardiac disease. Thus one may ascertain whether there is here anything to lead one to presume a structural change as producing the phenomena. When this is done it is found that far from supporting the hypothesis of a structural change, clinical observations tend definitely to rule it out. Thus many authors testify to the fact that when congestive heart failure appears in hyperthyroidism, there is usually some other organic factor, rheumatic carditis, syphilis, or the like, which tends to lower the cardiac reserve. Again, auricular fibrillation cannot be said to indicate, of necessity, structural alteration, for not only can it be produced with ease (as by asphyxia) in the laboratory without any ac-

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accompanying structural change, but together with other manifestations of serious cardiac embarrassment, it may, in the absence of co-existing organic heart disease, vanish literally overnight following satisfactory response to therapy.

In order to throw some light upon this problem with its mass of conflicting evidence, recourse has been had to two methods: first, examination of autopsy material together with full clinical records and autopsy protocols, and second, animal experimentation. In both cases what was believed to be an adequate number of control examples was studied. The results of these two investigations will be given separately.

AUTOPSY STUDIES

Twenty-seven autopsy cases were studied. Abstracts were made from clinical histories and autopsy protocols. Wherever possible, the gross autopsy material was examined and further microscopical preparations made for fat stains or routine haematoxylin and eosin stain. In every case sections of the heart and other important organs were available. The heart sections included, at least, part of the left ventricle, the mitral valve, and the left auricular wall. Positive findings in all other organs were recorded.

One hundred and fifty controls were studied; twenty-five for each of the six decades over which the cases of hyperthyroidism were scattered. These one hundred and fifty cases were chosen consecutively from the autopsy records, omitting cases of goiter, syphilis, profound anemia, septicemia, and local disease in and around the heart. Those cases in which coronary sclerosis was mentioned in the protocols were also discarded. Microscopical sections from the myocardium were examined in each instance.

The twenty-seven cases could be divided into three groups, according to the degree of alteration observed in the hearts. In none of the three groups was there any significant increase in the brown atrophy (lipochrome) granules. In the first group were fourteen cases in which the changes found were present also in normal hearts from the same age groups.

In the second group eight cases appeared, showing moderate changes such as intermuscular scarring or increased perivascular fibrosis, slight cell infiltration, and alterations in staining reaction or contour of muscle-fibers. Changes similar in kind, if not in degree and frequency, were found in normal hearts of the same age periods, which hearts had given no evidence of disturbed function during life. Because of their non-specific character and their occurrence in numerous control cases, it seems impossible to ascribe to these lesions the cardiac phenomena observed clinically. In both hyperthyroid and control cases all changes except the cell infiltration were more common in the later decades of life. It is conceivable that they may be accentuated as a result of prolonged

overwork in the presence of the profound metabolic changes demonstrable in the tissues of the hyperthyroid patient.

Finally, five cases fell into the third group. These exhibited profound changes, consisting of areas of muscle-fiber destruction with replacement by connective tissue, infiltration by lymphocytes and monocytes with occasional polymorphonuclear leucocytes. Old intermuscular and perivascular scars were sometimes seen. Of these five, three had co-existing organic heart disease, two rheumatic fever and one syphilitic aortitis, which might be held responsible for the lesions. In the other two there was nothing to account for the changes. One of them showed extreme diffuse change with destruction of muscle-fibers and mononuclear cell infiltration.

Out of the twenty-seven cases, definite hypertrophy occurred in sixteen. Dilatation was a frequent finding and might well explain the enlargement encountered clinically.

No satisfactory relation could be found between the clinical symptoms and the structural changes in the heart. Thus, of seven patients dying with congestive failure, two showed marked changes, two moderate changes, and three were normal. In both of those in which marked changes were present there was co-existent organic heart disease. Again, of the six patients with co-existing heart disease, five died with congestive heart failure and in only two cases was congestive failure present without organic cardiac disease. The duration of the hyperthyroidism bore no relation to the structural changes found in the microscopical preparations.

EXPERIMENTAL STUDIES

In the experimental work both rabbits and guinea pigs were used. Injections of thyroxin (Roche) were given intramuscularly on alternate days. Guinea pigs received doses of 0.1 to 0.17 mg. over 4 to 83 days; rabbits received doses of from 0.1 to 0.35 mg. over 2 to 13 days. The weight, temperature, and heart rate were recorded every day and the degree of hyperthyroidism judged by loss of weight, increase in cardiac and respiratory rate, diarrhea, apprehensiveness, and muscular weakness. Evidence of hyperthyroidism appeared usually thirty-six to forty-eight hours after the first injection and progressed with succeeding doses. Of the animals that died, only those so recently dead as still to be warm were included in the series. The majority were killed. Tissues were fixed in Zenker-formol or formalin. In every case both auricles and ventricles were examined and in most cases preparations were made from adrenals and lungs. In the case of both guinea pigs and rabbits, a series of normal hearts was examined in order to ascertain the variety and degree of changes present in the normal animal.

Seventeen injected guinea pigs were examined together with twenty controls. Of the seventeen experimental animals, nine were free from

apparent terminal infection and of these eight showed no lesions, while one, which singularly enough had given the least evidence of hyperthyroidism, showed a small area of dead muscle-fibers with lymphocytic infiltration. There was no other demonstrable change. It may be that this animal had an unrecognized area of lung infection similar to those found in the other eight animals in which almost identical cardiac lesions were found. These eight animals showed a spontaneous pneumonia due apparently to *Pasteurella bronchisepticus*. Moreover, all showed definite myocardial damage with masses of necrotic pink-staining muscle surrounded by monocytes and pseudo-eosinophils. In later stages this lesion was represented by areas of vacuolated and shrunken fibers with collapsed stroma, lymphocytes, and fibroblasts. Other lesions included an overwhelming proliferation of sarcolemma cells around degenerated muscle-fibers; also an extreme vacuolation of the muscle-fibers so that these appeared to be "blown out." One can only believe from these results that the hyperthyroidism *per se* produces at most very slight lesions, though it may have an adjuvant action, preparing the myocardium for the attack of any terminal infection or toxemia.

Forty-four injected rabbits were examined together with forty-three controls. The lesions found in 13.7 per cent of the controls (i. e., normal rabbits from stock) were surprising in degree and kind. The lesions in the experimental animals differed only in quantity and that slightly from those found in the control series. Here again one is forced to conclude that thyroxine, though given in amounts sufficient to render the animals markedly hyperthyroid, produces at most only insignificant morphological changes in the myocardium.

DISCUSSION

Both the autopsy and the experimental material therefore point to the fact that hyperthyroidism by itself produces no specific lesions in the myocardium. It is conceivable that damage produced on the one hand by physiological wear and tear and on the other by any associated infection or other disease tends to be more accentuated in the individual with hyperthyroidism than in the normal one. Whether such cases as those described by Fahr,⁴ Goodpasture,⁵ and Lewis,³ and occurring twice in the present series, in which profound damage is present without any co-existing complicating disease—whether such represent the results of a toxin derived from the thyroid gland and circulating in the blood, it is difficult to be certain. But the evidence at present points against the occurrence of a specific causal toxin producing specific myocardial lesions.

It is felt that in the past too much emphasis has been laid upon the morphological changes in the myocardium with consequent neglect of important alterations in the metabolism and function of the muscle-fibers. In this connection attention may be drawn to the recent work

on the glycogen content of voluntary and cardiac muscle in hyperthyroidism.^{6, 7} It has been shown that in the experimentally produced disease no glycogen can be found microscopically or by analysis in the myocardium. As a result of this, rigor mortis sets in immediately, a fact which the present authors can abundantly confirm from their experimental experience. It is well-known that the withdrawal of glycogen from cells normally well supplied with it renders them more liable to injury, injury to which they react by diminished function and actual structural change and death. This problem has been well examined in the case of the liver and one may well believe that similar reasoning can be applied to the myocardium. It seems more than probable that a close examination of this and other physiological problems will bring one nearer to the understanding of the cardiac abnormalities in hyperthyroidism.

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THE HEART RATE DURING SLEEP IN GRAVES' DISEASE AND IN NEUROGENIC SINUS TACHYCARDIA*

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A PERSISTENTLY rapid heart rate is one of the most characteristic features of Graves' Disease. It is caused chiefly by one or all of the following factors: The increased consumption of oxygen by the tissues which necessitates an increased minute-volume flow of blood to which the acceleration of heart rate contributes; the action of the altered thyroid secretion on the heart itself¹; the action of the altered thyroid secretion on the sympathetic nervous system leading to a neurogenic tachycardia superimposed on the basic acceleration determined by the first two factors.

The presence of an unexplained sinus tachycardia properly suggests the existence of Graves' Disease; yet in many instances such a rapid heart rate is due solely to neurogenic or psychogenic factors. Neurogenic sinus tachycardia is caused only by a disturbance of the nervous regulation of the heart, which interferes with the usual well regulated reflex adaptation of cardiac function to the needs of the body.

The determination of the basal metabolism is useful in distinguishing these two types of tachycardia, for only the thyrotoxic tachycardia is associated with an elevated basal metabolism. Although there is a close parallelism between the basal pulse rate and metabolism in successive observations on the same individual,² the relationship between the pulse rate and metabolism of different individuals is not so marked. The pulse rate cannot be taken as an absolute index of the activity of a given case of Graves' Disease, although an extreme degree of tachycardia suggests a greatly increased metabolism.³ A marked discrepancy, particularly the association of a slow pulse with a high basal metabolic rate challenges the accuracy of the basal metabolism estimation. A heart rate that is unduly rapid as compared to the basal metabolism is usually determined by reflex acceleration.

Another method of differentiating neurogenic from thyrotoxic tachycardia is by the determination of the minimum heart rate during sleep.⁴ I have shown elsewhere⁵ that the minimum heart rate during sleep is the best measure of the intrinsic chronotropism of the heart. The average minimum heart rate during sleep of normal males is 53, of females 58 a minute. In patients with Graves' Disease the high metabolism and the direct action of the thyroid secretion on the heart muscle persist during the full twenty-four hours. Reflex excitation by way of the

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unstable sympathetic nervous system diminishes greatly during sleep, so that with the abatement of these neurogenic overtones there will be a slight reduction in heart rate during sleep. The residual tachycardia is a rough measure of the degree of thyroid intoxication. A pure neurogenic tachycardia, on the other hand, almost disappears during sleep so that the figures approach those of normal individuals.

In this paper are presented studies of waking and sleeping heart rates recorded continuously with the eardiotaehometer⁶ of nine patients with Graves' Disease and ten with neurogenic sinus tachycardia. Observations were begun in the late afternoon and were continued through the night until the next morning. In a few cases the heart rate was recorded continuously for twenty-four hours. In Table I are recorded the minimum sleeping, and the basal heart rates, as well as the usual range of rate while awake.

TABLE I
HEART RATES

	CASE	MINIMUM SLEEPING	BASAL	USUAL RANGE WAKING	BASAL METABOLISM
<i>Females:</i>	A9	77	84	100	+28
Graves' Disease	A16	78	82	100 to 110	+23
	A4	79	86	90 to 100	+20
	A8	88	91	90 to 100	+33
	A17	98	106	110 to 120	+58
	A3	114	127	120 to 140	+77
	<i>Av.</i>	89	96		
Neurogenic	D2	64	112	100 to 130	
Tachycardia	D4	73	82	90 to 100	-2
	D5	53	73	90 to 100	
	D6	71	75	80 to 95	
	D7	64	70	85 to 100	
	D8	78	86	100 to 110	
	D10	59	73	90 to 100	
	<i>Av.</i>	66	81		
52 Normal cases	<i>Av.</i>	58	70		
<i>Males:</i>	A6	81	88	100 to 120	+36
Graves' Disease	A12	91	108	110 to 120	+55
	A13	95	105	110 to 120	+57
	<i>Av.</i>	89	100		
Neurogenic	D1	72	77	86 to 110	+13
Tachycardia	D3	62	68	80 to 110	
	D9	52	67	80 to 110	
	<i>Av.</i>	62	71		
51 Normal cases	<i>Av.</i>	53	61		

The patients with Graves' Disease have high minimum sleeping heart rates, over 30 beats a minute higher than those of normals. The minimum sleeping heart rate in general parallels the basal metabolic rate. The differences between the basal heart rate, and the minimum sleeping rate are rather small, demonstrating the slight reduction in rate during sleep. Although the range of heart rate of patients with neurogenic tachycardia during waking hours often approximates that of patients with Graves' Disease, during sleep the rate reaches minimum levels that approach those of normals. In this they differ sharply from the patients

with Graves' Disease. The table also shows that the minimum heart rate during sleep is a better guide than the basal heart rate in determining the significance of a given tachycardia. This is particularly well brought out in Case D2 in which the basal rate is 112 but the minimum sleeping rate is 64.

In these patients it is often difficult to obtain relaxation sufficient to permit accurate estimation of the basal metabolism and the basal heart rate. It is well known that basal metabolism estimations, unless performed with the greatest care, are apt to be too high. In such cases the determination of the minimum heart rate during sleep serves as an excellent check on the accuracy of the basal metabolism test. At times this record is obtained with difficulty, for patients with Graves' Disease often have a very light and restless sleep.

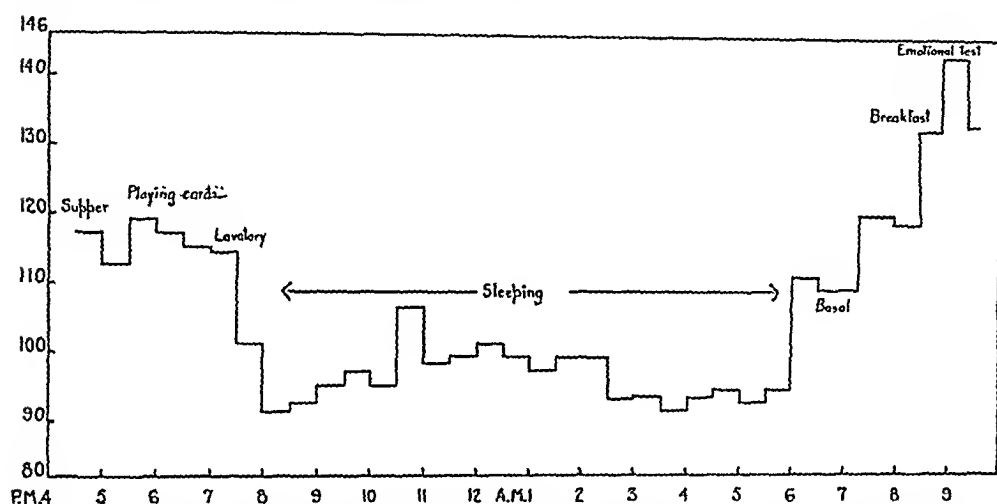


Fig. 1.—Seventeen hour record of heart rate of a man with Graves' disease. Basal metabolism + 55 per cent.

Fig. 1 represents a 17-hour record of the heart rate of a man with Graves' Disease. He had had mild symptoms for a number of years, which had become greatly aggravated during the preceding three months. His basal metabolic rate eleven days before the study of his heart rate was plus 55 per cent. The heart rate during sleep dropped to a minimum of 91, which is almost 40 beats higher than the average for normal individuals. Yet this minimum is low compared to his heart rate while he was awake, and in particular to his basal heart rate. It suggests that he was not fully relaxed at the time the basal heart rate and basal metabolism were measured.

Fig. 2 is the curve of heart rate of a negro woman with Graves' Disease, before and after operation. She, too, presented the classical symptoms of Graves' Disease. Her basal metabolism at the time of the first study was plus 28 per cent. Her heart rate, as observed at her visits to the clinic, ranged from 110 to 130. During the period of observation with the cardiograph the rate was lower and reached

a minimum of 77 during sleep, which, however, was 20 beats higher than the average minimum sleeping rate of normal women. Three and one-half months later, which was two months after subtotal thyroidectomy, the pulse was still rather labile but reached a minimum of 65 during sleep.

Fig. 3 represents the heart rate of a woman aged 49 who during a period of observation of over a year at the dispensary had always exhibited heart rates ranging from 112 to 150. She had no signs of

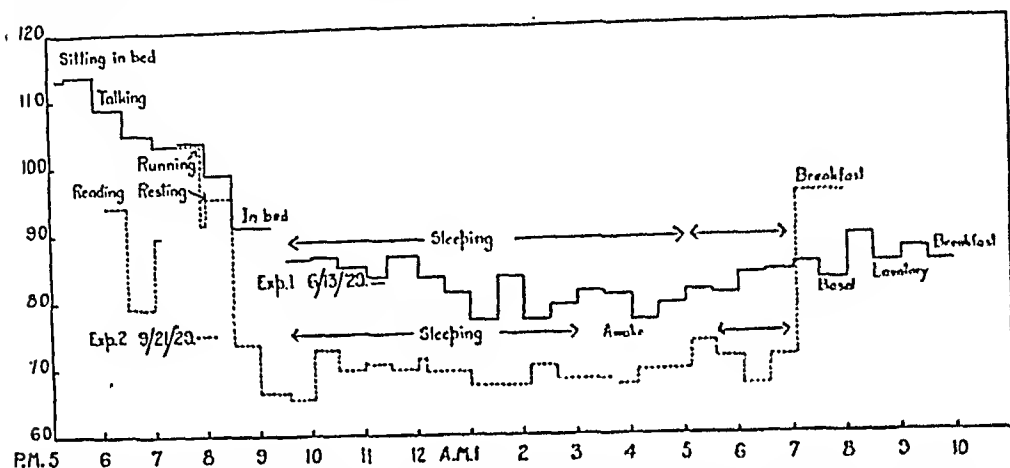


Fig. 2.—Curve of heart rate of a woman with Graves' disease. Solid line, basal metabolism + 28 per cent. Dotted line, two months after subtotal thyroidectomy.

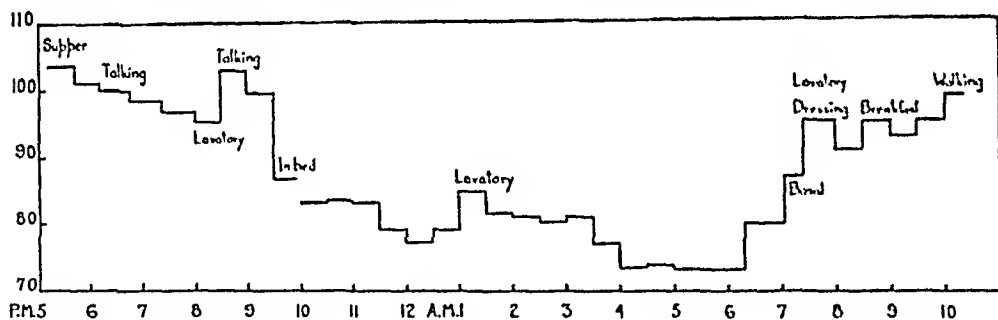


Fig. 3.—Seventeen hour record of heart rate of a woman with neurogenic sinus tachycardia.

Graves' Disease but had a mild systolic hypertension of about 160/80 with slight left ventricular enlargement, and a basal metabolism of minus 2 per cent. During her period of observation with the cardiotaehometer, when she was more relaxed and not so conscious that she was being observed, the heart rate did not reach the high figures that had been noted during her visits to the dispensary. It ranged round 100. During sleep it dropped to a minimum of 73. This case also illustrates the fact that in patients with neurogenic sinus tachycardia the heart rate during sleep does not descend to quite as low a level as in normal individuals. This point deserves further study, for it may offer a clue to the better understanding of the mechanism of this disorder.

SUMMARY

The heart rates of patients with Graves' Disease and with neurogenic sinus tachycardia have been studied with the cardiotaehometer. In Graves' Disease there is little reduction in heart rate during sleep, and the minimum sleeping rate is on the average over 30 beats higher than that of normal individuals. In neurogenic sinus tachycardia the heart rate shows a marked reduction during sleep, but does not quite attain the low level observed in normal individuals. The measurement of the heart rate during sleep is of diagnostic value in distinguishing thyrogenic from neurogenic tachycardias, and also serves as a rough check on the reliability of the basal metabolism determination.

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THE SIGNS AND SYMPTOMS OF HEART CHANGES IN TOXIC GOITER*

A CLINICAL STUDY OF 148 CASES

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THIS is a study of 117 cases of toxic goiter† which were observed in the Colorado General Hospital between February 24, 1925, and April 1, 1932, and of 31 cases seen in private practice in the same district and in practically the same period, a total of 148 cases received from the standpoint of signs and symptoms of heart involvement in toxic goiter. The Colorado General Hospital material was selected because it represents the combined records of the medical and surgical services of this institution and the work of eight attending physicians and surgeons with their staff officers. It thus represents a cross section of the observations of the average teaching hospital in this country, with due allowance for the fact that Colorado is not in a goiter area and that all of these patients lived at an average elevation of at least one mile above sea level.

In the tables relating to symptoms and signs other than pulse and blood pressure findings, and in their discussion, there has been no attempt to classify into types of goiter as exophthalmic and toxic adenoma, the presence of excessive or abnormal thyroid secretion being considered sufficient for inclusion in our series; where such a differentiation was made the biopsy diagnosis was accepted in all cases operated upon.

Sex.—There were 32 males and 116 females.

TABLE I

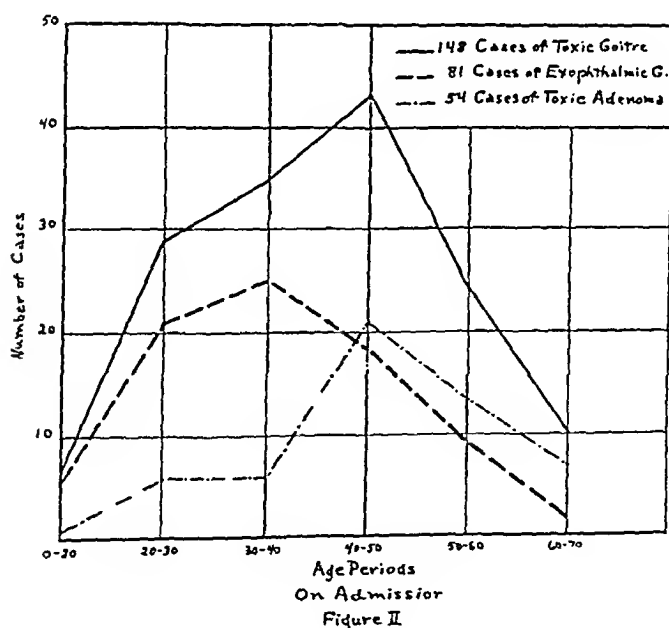
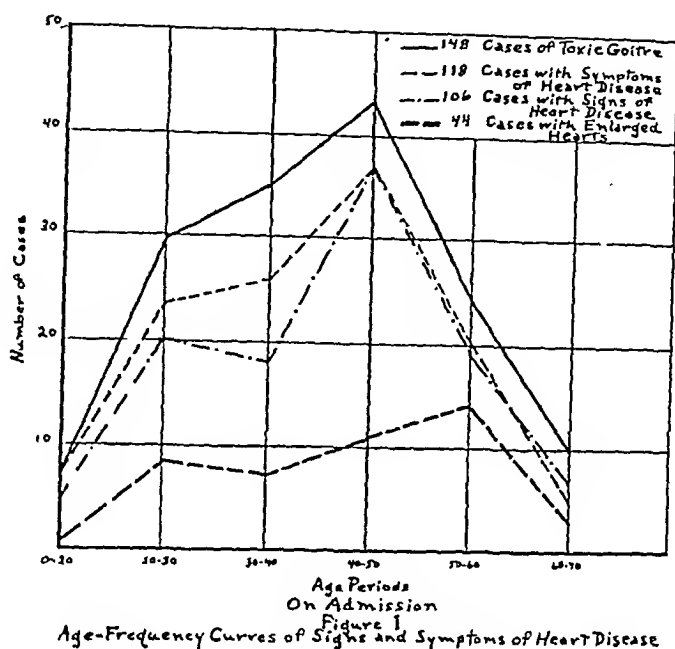
AGE DISTRIBUTION OF CASES SHOWING EXCESSIVE OR ABNORMAL THYROID SECRETION

	UP TO 20	20-30	30-40	40-50	50-60	60-70	TOTAL
Age when first seen	7	29	35	43	24	10	148
Exoph. goiter							
Age when first seen	6	21	25	18	9	2	81
Toxic adenoma							
Age when first seen	1	6	6	21	13	7	54
Mixed group							
Age when first seen		2	4	4	2	1	13
Signs of heart disease	5	20	18	37	19	7	106
Symptoms of heart disease	7	23	26	37	20	5	118
Large heart	1	8	7	11	14	3	44

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†Where the term toxic goiter appears in this paper, it refers to exophthalmic goiter or toxic adenoma of the thyroid, no attempt being made to differentiate the two types.

Age.—The average age of the males was forty-two years; the oldest was seventy and the youngest twenty-three. The average age of the females was thirty-nine years, the oldest being sixty-five and the youngest sixteen.



Thyrototoxic Symptoms.—The symptoms complained of, which could reasonably be ascribed to the dysfunction of the thyroid gland, quite aside from any resultant or co-existent heart disturbance, were as follows: nervousness, weakness, loss of weight, loss of strength, easy fatigue, tremor, sweating, flushing and sensations of warmth, increased

appetite, gastro-intestinal symptoms, eye symptoms, hyperpyrexia, emotional instability, insomnia and related manifestations of nervous irritability, swelling of the gland or neck, and such pressure manifestations as dysphagia, choking, cough, etc.

Symptoms of Heart Involvement in 148 Toxic Goiter Cases.—Dyspnea on exertion was the most frequently noted symptom, being present in 83 cases, or 56 per cent. Orthopnea was noted in 9 cases, or 6 per cent. Palpitation ranked next in importance, being present in 78 cases, or 53 per cent. Forty-seven cases (32 per cent) complained of tachycardia in addition to some other symptom usually accepted as indicative of heart disease. Next in order appeared swelling of the feet or ankles (37, 25 per cent), precordial or substernal pain (18, 12 per cent), heart consciousness (4, 3 per cent), dizziness (11, 7 per cent), and cardiac irregularity (5, 3 per cent).

In this series of 148 cases of thyrotoxic disease it was found that symptoms of heart disease appeared in 118 cases (approximately 80 per cent) in the following order of frequency:

TABLE II
HEART SYMPTOMS IN 148 CASES OF TOXIC GOITER
PERCENTAGE TABLE

Dyspnea or shortness of breath was complained of in 83 cases, of which orthopnea was noted in	83 9	56% 6%
Palpitation	78	53%
Tachycardia	47	32%
Swelling of ankles	37	25%
Precordial or substernal pain	18	12%
Dizziness	11	7%
Irregularity of heart	5	3%
Heart consciousness	4	3%

Signs.—Tachycardia was found on examination more than twice as frequently as complained of, being present in 107, or 72 per cent. This can hardly be accepted as a sign of heart involvement in toxic goiter, but merely as a measure of the physiological response to increased demands. The pulse was normal (70-90) in 23, 16 per cent, and slow (below 70) in one case.

The heart was noted as enlarged (indicated by the position of the apex beat, the percussion borders, x-ray, or any combination of these three methods) in 44, or 30 per cent; the average age of this group was 41.18 years. In 29 cases heart films were taken. In Table I and Fig. 1 it is seen that heart enlargement was noted chiefly in the fifth to sixth decades, although the peak of age incidence for the total series fell in the fourth and fifth decades (see Fig. 1).

A systolic murmur at the apex was noted in 59 cases (40 per cent); in Table III we present the available data as to transmission.

The systolic blood pressure was 160 mm. or above in 29 cases and the diastolic was 90 or above in 33 cases. The age periods in which these occurred is shown in Fig. IV.

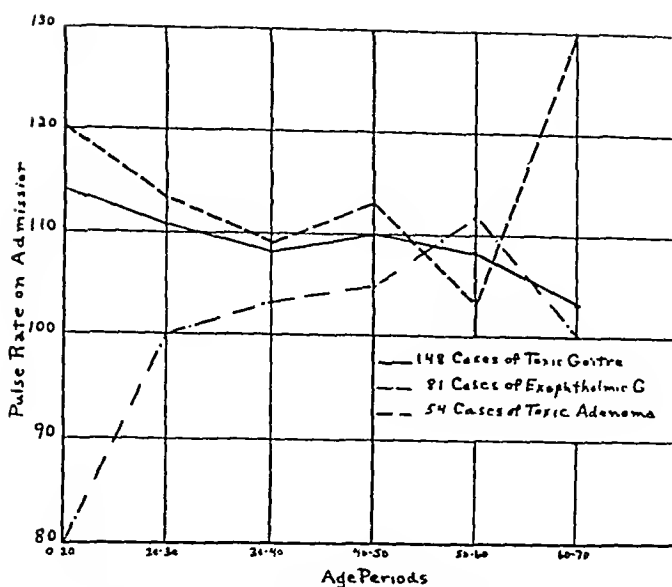


Figure III - Average Pulse Rates in Toxic Goitre by Age Periods

Number of cases at each age period.						Total	
T.G.	7	29	35	93	24	10	148
E.G.	6	21	15	19	7	2	81
T.A.	1	6	6	21	13	7	54

TABLE III

HEART SIGNS IN 148 CASES OF TOXIC GOITER PERCENTAGE TABLE

Normal heart, no signs other than tachycardia,	in 34 cases, 23%
Normal pulse, 70-90,	23 16%
Tachycardia, above 90,	107 72%
Heart enlarged	44 30%
Blood pressure, systolic 160 or above,	29 20%
diastolic 90 or above,	33 22%
Systolic murmur at apex or pulmonary area,	59 40%
Systolic murmur at apex or pulmonary area, transmitted,	24 16%
Systolic murmur at apex or pulmonary area, not transmitted	9 6%
Systolic murmur at apex or pulmonary area, no note as to transmission,	26 17%
Arrhythmia, total cases 36, 24%	
Auricular fibrillation	21 14%
Auricular flutter	2 2%
Arrhythmia, extrasystoles,	7
Arrhythmia, unclassified (no electrocardiogram)	6
Rheumatic heart disease, mitral (presys. or diast.)	6
Other abnormal signs	
First sound at apex, poor quality,	4
Rough first sound	3
Slapping sounds	3
Systolic shock	3
Artery sounds increased	3
Thrills, systolic and presystolic	3
Tic tac	1
Booming sounds	1
P ₂ accentuated	27 18%
Edema	11 7%
Liver enlarged	5
Cyanosis	3

Perhaps the greatest surprise was the infrequency of arrhythmia. This was noted in but 33 cases (22 per cent); of these there were 18 (12 per cent) of auricular fibrillation, 2 (2 per cent) of auricular flutter, and 7 (5 per cent) premature contractions. In 6 the disturbance was unclassified (no electrocardiogram.) Other less frequently encountered signs, occurring independently or in association with one or more of the previously discussed signs, are presented with their frequency of

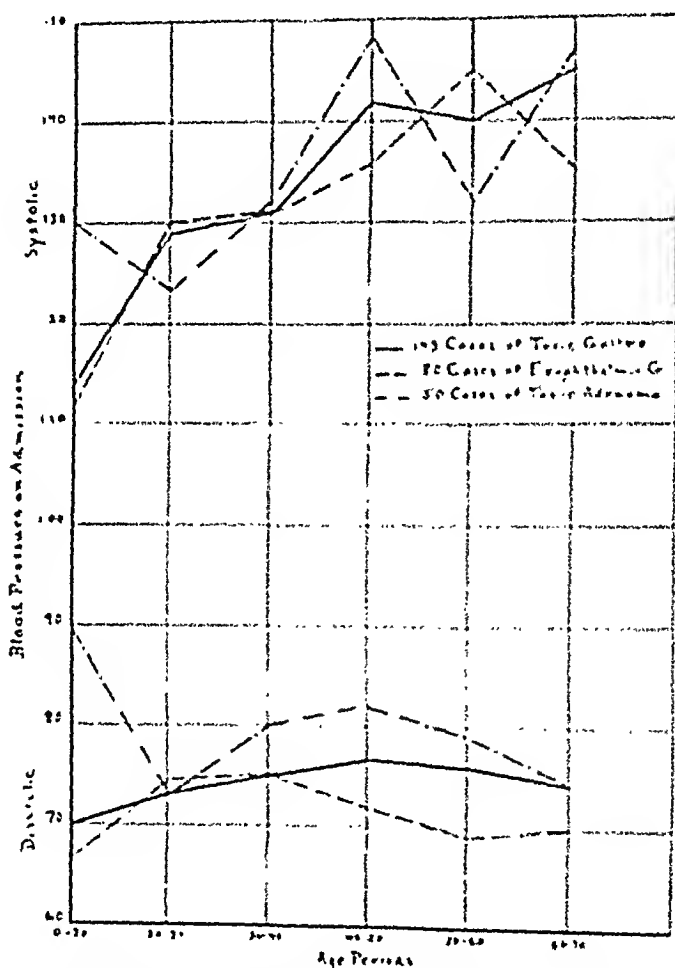


Figure IX—Average Blood Pressures in Toxic Goiter, by Age Periods

Age Period	20-30	30-40	40-50	50-60	60-70	Total
TC	6	25	47	35	11	124
EG	20	25	17	16	2	80
TA	4	5	20	13	7	59

incidence in Table III. Excluding tachycardia, the heart was found entirely normal by every means of examination employed in the individual case in 34 patients (23 per cent). In some cases this was determined only by the usual means of physical examination, in some by x-ray and the electrocardiogram.

Signs of decompensation occurred in only 19 (13 per cent) cases; in these there was dependent edema in 11 (7 per cent), the liver was enlarged in 5 (3 per cent), and there was cyanosis in 3 (2 per cent). The

TABLE IV
HEART SIGNS AND SYMPTOMS BY DECADES AND ACCORDING TO THE DURATION OF SYMPTOMS

	UP TO 20		20-30		30-40		40-50		50-60		60-70		TOTAL	TOTAL
	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.
0 to 3 mo.	1	1	1	2	3	4	6	6	2	2			13	15
3 to 6 mo.		1	2	2	1	1	1	1					4	5
6 to 9 mo.			2	2	3	3	4	4	3	4			12	13
9 to 12 mo.	2	2	5	5	4	5	11	10	2	2	2		26	26
2nd year	1	1	4	4	4	5	6	6	3	3	1		19	19
3rd year	1	2	2	3		1			5	5			8	11
4th year				2			2	2	2	2			4	6
5th year						1					4	2	4	3
5th-10th year			2	1	2	2	1	1	1				6	4
10 years and more			2	2	1	4	5	6		1	1		8	14
Duration not determinable							1	1	1	1			2	2
Total	5	7	20	23	18	26	37	37	19	20	7	5	106	118
Auricular fibrillation					2		10		5		4		21 cases	
Congestive heart failure			4		2		5		6		2		18 cases	
Heart signs persisting after thyroidectomy			1		1		6		3				11 cases	

Criteria: Signs—more than tachycardia alone; e. g., heart enlarged, murmurs, B. P. +, edema, EKG abnormal, etc.
Symptoms—more than tachycardia; e. g., dyspnea, pain, palpitation, etc.

pulmonary second sound was accentuated in 27 (18 per cent). Whether this is indicative of anything more than the toxic effect on the heart, or whether it is an indication of early decompensation is a matter for debate.

Period in Thyrotoxicosis at Which Heart Signs and Symptoms First Appear.—Reference to Table IV shows how frequently both signs and symptoms of heart involvement occur in the early months of thyroid intoxication. Examination of Fig. I shows that this appears to be about proportional to the age distribution of our cases.

Pulse.—An attempt to study the pulse and blood pressure records of these cases indicated the need of determining the relative age incidence of the cases of exophthalmic goiter and toxic adenoma in this series. Fig. II shows that in the first group of cases the peak is reached in the fourth decade, while in the second group it is reached in the fifth decade, a finding entirely in accord with previous observations.

Employing the same method of study, it is found by reference to Fig. III that, if we compare the pulse records between the ages of twenty and sixty years, the pulse rates in exophthalmic goiter are considerably higher in the third and fourth decades than in toxic adenoma, that the curves cross in the fifth decade, the toxic adenoma cases showing a higher rate than the exophthalmic cases, and that the curves again cross in the sixth decade, the adenoma cases showing a steady decline in pulse rate. Our series presented only two cases of exophthalmic goiter in this decade, one a fibrillator with a rate of 170, the other with a regular rate of 90.

A similar comparison of the systolic and diastolic blood pressure of exophthalmic and toxic adenoma cases shows (see Fig. IV) that the systolic pressures in these two types, while fairly parallel, are inconstant. The diastolic pressure curves show a slight but constant elevation in the adenoma group.

Electrocardiogram.—An electrocardiogram was made in 62 cases of our series. Slurring of the R-wave was noted in 46 instances, and the most striking deviation from the normal was the occurrence of slurring in all three leads in 18 cases (29 per cent of the curves). Axis deviation occurred in 24 cases, to the right in 7 and to the left in 17 cases. The type and frequency of arrhythmias have been discussed earlier in this paper. Notching of the P-wave occurred in 25 cases (40 per cent of the curves). It was observed in all leads but notably in Leads II and III.

Antecedent Rheumatic Infection.—It was found that definite signs of rheumatic carditis occurred in 6 of the 148 cases of toxic goiter. This finding invalidates to this extent the notation of heart findings as a part of the thyroid heart picture.

This study emphasizes the desirability of the adoption of the standards of the American Heart Association by the various hospitals where there is any hope for the utilization of records for later statistical and clinical study.

DISCUSSION

Criteria.—We have excluded tachycardia as evidence of involvement of the heart other than as evidence of increased demands. We feel that the remaining criteria, some of which admittedly are at times noted in conditions where there is no evidence of heart involvement, in general are accepted as evidence of heart disturbance at least of a functional type. In a preliminary grouping of toxic and non-toxic goiter in a series of 196 cases we excluded many cases from the toxic group because there appeared to be some question as to true thyroid toxicity; therefore we believe this presentation of heart signs and symptoms in toxic goiter is accurate within the limitations of the number of cases presented.

Detailed Discussion of Symptoms of Heart Involvement in Toxic Goiter.—Dyspnea occurred slightly in excess of any other symptom (56 per cent). We were surprised to note that this symptom was complained of more frequently than tachycardia or palpitation.

Palpitation ranked next in frequency (53 per cent). Numerous authors have emphasized the importance of this symptom. Kerr and Hensel¹ believe that this very often represents a transient auricular fibrillation or flutter.

Dependent edema was complained of in 25 per cent and noted on examination in 7 per cent of our cases. Willius, Boothby and Wilson² noted this in one-fifth of their cases. This was the only symptom noted which was especially associated with congestive heart failure and it is of interest that 25 per cent of our cases, which we considered had symptoms and signs of heart disease, complained of swelling of the legs or feet.

Precordial or substernal pain was noted by 12 per cent. Dameshek³ records this in 13.5 per cent of his series of 141 cases. The frequency of precordial pain in neurotic states and the recognized effect of the thyroid toxin on the nervous system renders this as a sole symptom of heart disease of very doubtful value; however, no cases included failed to show some other symptom of heart disease. In an undetermined number of the older patients cardiosclerosis may have been a factor, although we have no electrocardiographic evidence on this point. Certainly pain cannot be considered a common symptom in thyrotoxicosis.

Vertigo was complained of in 7 per cent of the cases, and an additional 3 cases complained of fainting attacks. Since the average age of the patients experiencing vertigo was 39 years, this can hardly be attributed to arteriosclerosis. The average systolic blood pressure in this group (vertigo cases) was 134 mm., the average diastolic was 79, and the average pulse pressure was 55, which would seem to indicate that some factor other than cardiac was the basis of vertigo in these cases. We suggest vasomotor instability associated with thyrotoxicosis as a more probable explanation.

Cardiac irregularity was complained of by 3 per cent of the patients, although it was noted in 22 per cent. In view of the recognized neurotic

tendency of these patients it is interesting that this striking symptom was not more frequently mentioned by the patient.

Heart consciousness was spoken of by only 4 patients in addition to the 18 who complained of pain, a point of interest as noted in the preceding paragraph in connection with cardiac irregularity in this type of patient.

We noted symptoms of heart disease in 118 of the 148 included cases, whereas *signs* were noted in only 106 of these. Willius² and his associates state: "The most outstanding fact is the infrequency in both types (exophthalmic and adenoma) of symptoms indicating the heart." No doubt their criteria were more rigid than ours. Kerr and Hensel¹ noted more or less marked cardiovascular symptoms in 44 per cent of 181 goiter patients, but of their cases approximately 50 per cent of the adenomas were considered non-toxic, reducing thereby their toxic series to about 148 cases, in other words, a group numerically similar to ours. Their figure of 44 per cent of cases showing cardiovascular symptoms should then be corrected to 65 per cent of the toxic cases in comparison with our figure of 79 per cent.

We were unable to note any difference in the symptoms in the two types, but such difference as seems to exist appeared to depend upon the age of the patient, duration of symptoms and the condition of the heart at the moment of the onset of the toxic insult.

We considered a heart normal if there were no physical, x-ray or electrocardiographic signs of abnormality other than tachycardia. Dameshek³ has employed less rigid criteria for the normal heart in that he has considered a blowing systolic murmur (no note as to transmission) as a normal heart finding. With our standard we found 23 per cent in which there are no signs of heart abnormality.

Our standard for a normal pulse rate, 70 to 90, may be criticized; but it should be noted that all of these patients were residing at the time of observation at an altitude of one mile above sea level, where an increase in heart rate of at least ten beats per minute as compared to sea-level standards is considered well within normal, and rates of 85 to 90 are so frequently encountered in the normal individual that it seemed wise to establish this wide range of 70 to 90 per minute.

We feel that we do not possess satisfactory evidence regarding the duration of toxic symptoms in relation to heart enlargement, but we show that demonstrable heart enlargement occurred in 30 per cent of our cases and notably at the later ages in which thyrotoxicosis occurs (see Fig. I). A study of Figs. I and II suggests that toxic adenoma bears a greater causal relationship to enlargement than does exophthalmic goiter.

We made a study of enlargement in reference to the duration of symptoms, existing murmurs, etc., in an attempt to learn in what proportion of the cases enlargement was probably due to hypertrophy and what

proportion due to dilatation, but we were unable to arrive at any conclusion. We found enlargement without electrocardiographic evidence of myocardial damage, a point previously noted by McEachern and Rake.⁴

We noted apical systolic murmurs (40 per cent) much less frequently than shown by Dameshek,³ who stated that only 10 to 15 per cent failed to show a loud, blowing systolic murmur. Willius² and his co-workers noted murmurs in nearly one-half of their cases. Excluding 6 cases of probable preexistent rheumatic endocarditis, we had 18 cases or 12 per cent in which the apical systolic murmur was found to be transmitted. Willius,² et al., classed these apical murmurs with a variable transmission as probably dilatation murmurs, a view with which we agree in the majority of cases.

Signs of congestive heart failure were noted in 13 per cent and in both exophthalmic goiter and toxic adenoma. Four cases occurred in the absence of auricular fibrillation.

Our records do not corroborate former statements as to blood pressure in goiter. Willius,² et al., stated that in exophthalmic goiter the pulse pressure is increased. We did not find this to be the case in the early decades; but there is this tendency in the later decades, although even at that period it is not striking. In adenoma the average diastolic pressure reaches a peak at between forty and fifty years, which is also the peak of the age incidence in our series; and at the same period the highest average systolic pressures are recorded. We do not feel that we are justified in making any general statement as to blood pressure in toxic goiter, other than that in toxic adenoma there does appear to be a substantial increase in the diastolic pressure.

Other Abnormal Signs.—A variety of signs frequently noted in connection with cardiovascular changes associated with thyrotoxicosis are listed in Table III. Rough and impure first heart sounds might well have been described by some other observer as systolic or presystolic murmurs, a fact to be borne in mind in the differentiation of mitral stenosis and the hyperthyroid heart. So far as we could ascertain, none of these presented other evidence, historical or physical, of rheumatic heart disease. The slapping and booming sounds and systolic shock together with increased artery sounds all denote an overactive heart and form part of the clinical picture of hyperthyroidism, but whether they indicate more than simple overactivity remains to be proven. Smith and Colvin⁵ incline to the view that these sounds are indicative of hypertrophy when noted in the absence of definite signs of aortic insufficiency. It is possible that some of the 6 cases, which we grouped as rheumatic heart disease associated with toxic goiter, may have been instances of marked vascular phenomena of hyperthyroidism.

Arrhythmias.—Next to persistent tachycardia the most striking heart sign in toxic goiter is the evidence of auricular fibrillation. Certain

authors state that this is a purely functional condition—a statement difficult to disprove in certain instances, but its frequency in toxic goiter (our series 14 per cent; White⁶ about 20 per cent) strongly suggests a profound, though possibly transient, change in the heart muscle.

The Electrocardiogram in Toxic Goiter.—In only a few instances were later or post-operative curves made; hence we have no means of determining whether the changes noted were transient or permanent.

While R-wave slurring near the base line may occur in normal tracings, it is generally accepted that slurring of the R-wave in all leads is never normal, and we found 29 per cent of the curves presenting this abnormality. Left axis deviation in 27 per cent of the curves is probably explained by the long continued cardiac overload maintained by these cases. Right axis deviation was noted in 7 cases. Pardee⁷ considers this is a proof of mitral stenosis. Six of our goiter cases also presented clinical evidence of mitral stenosis.

Smith and Colvin⁵ in a series of 100 hyperthyroid cases found a definite increase in the P-wave. With this observation we do not agree. We noted notching of the P-wave in 40 per cent of our curves. This is an incidence only slightly higher than that noted by Pardee, who stated that about one third of normal cases will show this change. A study of a larger series would seem desirable.

Several authors have noted T-wave changes, notably increased amplitude, which they considered specific. Our curves do not substantiate this. We have not noted increased amplitude of the R-wave as reported by certain authors.

We found definite electrocardiographic evidence of myocardial change, in addition to the disturbances in rhythm in a sufficient number of cases to warrant the conclusion that myocardial damage does occur in toxic goiter. We did not find any electrocardiographic sign or signs which we consider specific in toxic goiter.

SUMMARY

We have shown that about one third of our cases had enlargement of the heart at the time of examination; in some of these we have reason to believe this was persistent, but are unable to present figures on this point. We found apical murmurs in two-fifths of the cases. Since some apical murmurs persisted after the clinical improvement of the patient, we concluded that at least some of these were not due solely to cardiac dilatation.

A summary of all cases presenting signs of heart disturbance reveals that 106, or 71 per cent, showed some sign exclusive of tachycardia during the toxic state. In 11 cases (7 per cent) definite heart signs persisted after recovery following thyroidectomy. These observations lead us to conclude that at least temporary heart damage is present in approximately two thirds of the cases during the toxic stage and that in a

small group this damage is permanent. Others have presented theories and substantiating evidence as to the cause of this damage; but whether or not observers admit heart damage in toxic goiter, all agree that the cardiac manifestations occupy the center of the stage in the vast majority of the severe cases.

CONCLUSIONS

That the heart is gravely involved in the course of goiter intoxication is evident; that in the average case it is permanently damaged is neither proved nor disproved by these records. The fairly large number (46 per cent) of individuals in whom the condition after operation, with a resultant drop in the basal rate, is either not improved or is doubtful, and in whom the pulse rate remains somewhat elevated (above 90 in 33 cases) and dyspnea of some degree persists, strongly suggests that the heart has not fully recovered from the toxic insult; but nothing is presented in this study to prove the nature of this damage. It would seem that one is not dealing entirely with the "old heart" in these cases, but that at any age the toxins associated with goiter may so affect the heart as to cause some degree of permanent damage.

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(For discussion, see page 144.)

A CLINICAL STUDY OF GOITER IN THE PACIFIC NORTHWEST, WITH SPECIAL REFERENCE TO THE STATE OF THE HEART*

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FOR a number of years it has been known that endemic goiter prevails in the Pacific Northwest. From sporadic surveys¹ and from the results of the draft examinations it has been thought to be more frequent in this locality than in any other section of the United States. Surveys, however, conducted by the Public Health Service² would indicate that its incidence of goiter is less than that of Minnesota, in which region goiter finds its greatest frequency. The region of the Pacific Northwest embraces in general that part of the United States and Western Canada within and supplied more or less by the water sheds of the Cascade Mountains. It therefore includes Oregon, Washington and British Columbia and portions of Idaho and Montana. Utah and Wyoming also have a comparatively high incidence, and when added to that of the Cascade Mountain district, gives to the entire series an incidence varying between 10.01 and 27.00 per 1000 of population. A local survey among children of public school age in Oregon³ revealed nodular goiter in 1.8 per cent of the boys and in 4.1 per cent of the girls. The cause of the high incidence of goiter in this region has been generally attributed, especially since the studies of McClendon and Hathaway,³ to the low iodine content of the water which is used not only for drinking purposes but also for the irrigation of vegetable gardens and orchards. The water supply of the city of Portland, for instance, is from Bull Run Lake, of glacial origin, which lies at the foot of Mount Hood, and contains from 0.03 to 0.10 parts iodine per billion parts of water. In comparison the water of New York City contains 2.50 parts iodine per billion parts of water, and that of Stanford, California, 105.8 parts iodine per billion parts of water.

In the present paper we have analyzed a series of goiter patients studied and operated upon in the Portland Clinic during the years 1925, 1926 and 1927. Approximately 1500 patients with goiter were registered in the clinic during these years, of which number 1066 came to operation because of various surgical indications. Of the latter number 835 have been analyzed from the standpoint of the heart and the associated pathological structural changes in the thyroid because sufficiently accurate clinical data were noted in the histories to make such an analy-

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Read by Title.

sis possible. The majority of these cases belonged to the toxic nodular and the varying mixtures of the hyperplastic groups. Some nodular enlargements with normal basal metabolic rate and normal heart action were removed because of pressure symptoms and for cosmetic reasons. The patients themselves, with few exceptions, came from diverse places within the Cascade Mountain district and represent quite accurately therefore the types of goiter with symptoms found in this locality.

In the analysis of the patients an attempt has been made to obtain a reasonably accurate idea of the presence or absence of cardiac enlargement, of cardiac failure, and of auricular fibrillation in relation to age incidence, hypertension, basal metabolic rates, associated cardiopathies and the type of the goiter present. Cardiac enlargement was determined in some instances by orthodiagraphic measurement before the fluoroscope or from the seven-foot plate. Both methods are relatively inaccurate; their results do not check well on repetition. Many more instances were determined by percussion measurements on the chest wall and the location and character of the maximal thrust of the apex of the heart alone. The latter method is quite as satisfactory as the former. Cardiac failure before the beginning of congestive signs is oftentimes difficult to recognize. It undoubtedly existed many more times than are recorded in the tables. After dilatation of the right heart takes place and evidence of passive congestion is manifest, the most serious of the complications of thyrotoxicosis is present. Its significance depends, of course, upon the heart's response to preoperative treatment directed toward the failure, which, in turn, depends mainly upon the state of the myocardium and associated cardiac lesions, and not upon the duration or the degree of the failure itself. The character of the structural changes in the myocardium of the goiter patient suffering from thyrotoxicosis, and whether these changes are specific for the disease, is the problem of paramount importance which remains yet to be solved. It will not be determined by clinical studies, nor in all probability from human heart material. The presence of a related cardiac syphilis, a rheumatic heart lesion, or a cardiovascular hypertensive disease may influence the occurrence of fibrillation and of failure, but such diseases mask rather than clarify the question as to the cause of the peculiar toxic type of heart action which most clinicians of experience are agreed is not duplicated by other toxic agents. The problem must be solved, if ever, by animal experimentation and the reading into the human problem of those findings which seem to have a bearing upon the heart's action of the experimental animal.

For many years the classification of goiters has been made the subject of much study. For some time past we⁴ have grouped the portions of glands removed at operation and the whole glands obtained at autopsy according to their gross pathological characteristics and predominating microscopic pathologic structures in a manner which agrees essentially

with the clinical classification now adopted by the American Association for the Study of Goiter. It is as follows:

- I. Diffuse parenchymatous hyperplasia—marked increased activity.
 - (1) Gross observations: Gland compact, vascular or ischemic, grayish to pinkish white and colloid-free.
 - (2) Microscopic observations:
 - (a) Hyperplasia and hypertrophy of epithelium.
 - (b) Peripheral or general vacuolization of colloid.
 - (c) Dilatation of lymph channels and engorgement of blood vessels.
 - (d) Variable increase in the supporting stroma with or without round-cell infiltration.
- II. Disseminated adenomatous hyperplasia—normal or moderately increased activity or no activity.
 - (1) Gross observations: Gland diffusely reddish-brown without noticeable nodularity or accentuation of lobular markings; a variable amount of colloid and pinkish to yellowish gray opacities.
 - (2) Microscopic observations:
 - (a) Focal changes similar to those in group I.
 - (b) Normal or colloid-distended alveoli.
 - (c) Focal hyperplasia and hypertrophy of epithelium.
 - (d) Intervalveolar hillocks or intra-alveolar papillomatous projections.
 - (e) Focal collections of round cells or pseudolymphnodes.
 - (f) Focally increased vascularity and dilated lymph channels.
 - (g) Focal fibrous increase of connective tissue.
- III. Nodular adenomatous hyperplasia—subnormal, normal or moderately increased activity.
 - (1) Gross observations: Variable nodular accentuation of the lobular markings with or without excessive storage of colloid cystic degeneration, hemorrhage, scarring or deposit of lime salt. The color usually varies with the regressive changes.
 - (2) Microscopic observations:
 - (a) Focal changes similar to those found in groups I and II and compensatory.
 - (b) Characteristic retrogressive changes.
 - (c) Areas of adenomatosis.
- IV. Solitary adenoma.
 - (1) Gross observations: Adenoma variable in size, circumscribed, solitary or multiple, grayish-white to dark reddish-brown, solid and cystic or colloid-filled. Regressive changes may be present.
 - (2) Microscopic observations:
 - (a) All stages of fetal types of alveoli.
 - (b) Peripheral formation of pseudocapsule with round cell infiltration and compressed alveoli.
 - (c) Focal hyperactive areas in adjoining parenchyma.
 - (d) Adjacent areas of adenomatosis.

It will be observed in this grouping of thyroid diseases on the basis of the gross anatomical characteristics that the basic histological changes which bear evidence of increased secretion are essentially the same. That is to say, regardless of the gross alterations we recognize no specific disease entities of the thyroid. All hypersecretion is considered fundamentally one and the same process differing only as it is influenced by

extent, degree, age, other intercurrent diseases, and its effect upon other glands of internal secretion. The correlation of such a pathological anatomical grouping with the symptoms has been shown in a previous discussion.⁵

While the above outline permits a satisfactory pathological grouping of the various toxic goiters we meet, there are many instances seen in which several groups are represented in the structural picture of one gland from a pathological viewpoint and some others which clinically do not fit into the pathological group to which they are expected to belong. However, a certain degree of increased activity has been recognized in all of the glands belonging to the present series of cases, and, in a general way, it follows quite closely the degree of toxic heart action experienced by the patient. The heart action, incidentally, has been of more value in the recognition of mild thyrotoxicosis than all other symptoms.

For the clinical analysis of the cases in the series we follow, not the above pathological grouping, but a similar clinical classification, as follows:

1. Diffuse goiter (a) nontoxic (b) toxic. 2. Nodular goiter (a) nontoxic (b) toxic. We have also attempted to divide the diffuse toxic type of goiter according to the pathological picture into (a) diffuse parenchymatous goiter—true Graves' disease, and (b) diffuse adenomatous goiter. This distinction cannot be sharply drawn, for many glands of each group show both parenchymatous and adenomatous hyperplasia in varying degrees. Clinically, however, the cases are often distinct, for the one is more frequently seen in younger persons with acutely fulminating symptoms, whereas, in the other case the person is usually older—he has known of the presence of a goiter for a long time, and his thyrotoxic symptoms are less marked. Since the recognition of the use of iodine prophylactically and therapeutically, greater difficulty is encountered in separating these groups clinically and pathologically. It is now unusual for the pathologist to observe a thyroid gland with the characteristic findings of exophthalmic goiter.

In the table of general data (Table I) one notes, as has been observed by others before, that heart lesions in thyrotoxicosis appear most frequently in the middle and later decades of life. Its pathology is not an accepted entity; it may not be at all specific, although the occurrence of enlargement and auricular fibrillation in patients in the twenties may suggest a specificity. What have been considered to be specific lesions of the myocardium in experimental animals have been described by Goodpasture,⁶ Cameron and Carmichael,⁷ Hashimoto,⁸ and Takane.⁹ Other investigators have denied significance to such findings. We have observed in experimental rabbits,¹⁰ to which had been administered thyroid extract, thyroxin and desiccated gland substance from human hyperplastic glands, monocyte, plasma cell and eosinophile invasion, fat

TABLE I
RÉSUMÉ OF 835 CASES OF GOITER IN THE PACIFIC NORTHWEST WITH REFERENCE TO THE STATE OF THE HEART*

		MALES 148—PERCENTAGE 17.7: FEMALES 687—PERCENTAGE 82.3				
		AVERAGE AGE—MALES 45.5 (18 TO 74 YEARS): FEMALES 40.5 (14 TO 81 YEARS)				
	AVERAGE BLOOD PRESSURE	AVERAGE BASAL METABOLIC RATE	KNOWN DURATION OF GOITER	CARDIAC ENLARGEMENT AGE INCIDENCE	CARDIO FAILURE AGE INCIDENCE	AURICULAR FIBRILLATION AGE INCIDENCE
Group 1	136 — 81	+5	12 years	12 = 11% 20-29 = 0 30-39 = 1 40-49 = 2 50-59 = 5 60-69 = 3 70-79 = 1	0	0
a. Nontoxic Nodular 109 Cases						Sclerosis 7 Cardio-renal 4
b. Toxic Nodular 359 Cases	148 — 81	+32	13 years	93 = 25% 20-29 = 3 30-39 = 14 40-49 = 16 50-59 = 35 60-69 = 19 70-79 = 6	20 = 5.5% 40-49 = 1 50-59 = 13 60-69 = 5 70-79 = 1	18 = 5.0% 40-49 = 3 50-59 = 9 60-69 = 6
						Sclerosis 26 Cardio-renal 50 Rheumatism 2 Syphilis 2
Group 2	140 — 81	+1	6 years	2 = 6.4% 50-59 = 1 60-69 = 1	0	0
a. Nontoxic Diffuse 31 Cases						Sclerosis 2
b. Toxic Diffuse 328 Cases	143 — 79	+39	3½ years	115 = 35.1% 20-29 = 15 30-39 = 35 40-49 = 36 50-59 = 17 60-69 = 11 70-79 = 1	26 = 7.9% 20-29 = 3 30-39 = 7 40-49 = 7 50-59 = 6 60-69 = 3	21 = 6.4% 20-29 = 3 30-39 = 2 40-49 = 5 50-59 = 10 60-69 = 1
						Sclerosis 20 Cardio-renal 14 Rheumatism 6 Syphilis 1

*The series includes 8 cases of carcinoma of the thyroid—1.2 per cent.

vacuole formation, moderate fibroblast increase and fraying of the muscle bundles. The control animals did not show these changes. The same lesions, including the fraying of the muscle fibers, were also observed in one rabbit which lived for six days after a bilateral sectioning of the depressor nerves and the destroying of the carotid sinus investments. A continuous tachycardia was produced by this procedure and thyroid substances were not administered. This single observation—it is difficult to keep such animals alive after such a surgical procedure—suggests the possibility that the change in the structure of the heart muscle is a traumatic and inanition effect due to the heart's racing. Considered in this light the long continued tachycardia of thyrotoxicosis may have a like effect, in which case the lesion should be considered clinically quite as much an entity as though produced by toxemia. The effect of advancing age is seen, also, in cardiac syphilis, in cardiorenal disease and chronic atherosclerosis, and failure occurs in them most frequently during the middle decades of life. The age element does not argue against the specific nature of these diseases. The association of other heart lesions is seen many times, particularly sclerosis and chronic hypertension, and the addition of this new factor may have added merely a greater load to the heart and another character, which can be recognized as more or less distinct from the underlying thyroid heart disease. Such associated factors undoubtedly hasten cardiac failure and make the ultimate recovery of the heart after thyroidectomy more problematical. Again, auricular fibrillation, paroxysmal and persistent, is seen more frequently in thyrotoxicosis than in any other form of heart disease. So significant is its presence in a person under fifty that the diagnosis of toxic goiter is at once considered probable. The suggestive evidence, in like manner, of the peculiar, quick, forceful thrust of the heart's beat, never seen in other heart diseases, leads one to the same conclusion. Three times in our experience has this type of heart action led to the exploration of the neck in patients in whom no palpable evidence of goiter could be recognized, and in each instance a small adenoma with hyperplasia was found.

Auricular fibrillation occurred in this series of cases 39 times or 4.7 per cent, a much smaller percentage than reported by Parkinson and Cookson¹¹ (27 per cent in 130 cases). The reason for this variance lies in the material studied. In any region in which goiter is endemic the inhabitants become goiter minded and seek surgical relief early. For this reason the majority of our patients were seen and operated upon before serious cardiac complications had developed. During the years embraced in the series; namely, 1925, 1926 and 1927, we were more cautious about the use of quinidine than we later became and the patients were not then treated as we treat them now. At that time we insisted upon a month or more passing after the operation before quinidine therapy was attempted. In the meantime many patients had

TABLE II
AURICULAR FIBRILLATION IN TOXIC DIFFUSE GOITER, DIFFUSE ADENOMATOUS TYPE, 10 CASES

END-RESULTS

AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	RELIEVED BY			RELAPSED	PERMA- NENT	REMARKS
						OPERATION	STRO- PHANTHIN DIGITALIS	QUINIDINE SULPHATE			
37	F	Thyroid	$\frac{190}{100}$	5 months	+	+	-	-	-	-	-
48	M	Thyroid	$\frac{140}{85}$	7 months	+	-	-	-	-	+	-
59	F	Sclerosis Thyroid	$\frac{170}{100}$	4 months	+	+	-	-	-	-	-
62	M	Sclerosis Thyroid	$\frac{136}{70}$	6 months	+	Followed op- eration by several months	-	-	-	+	-
53	F	Sclerosis Thyroid	$\frac{200}{95}$	1 month	+	Paroxysmal	-	-	-	-	-
23	F	Thyroid	$\frac{180}{80}$	1 year	+	Paroxysmal	-	-	-	-	-
40	F	Thyroid	$\frac{140}{70}$	1-2 years	+	Paroxysmal	-	-	+	-	-
55	F	Sclerosis Thyroid	$\frac{190}{110}$	2 years	+	-	-	-	-	+	-
56	F	Sclerosis Thyroid	$\frac{216}{90}$	-	+	Followed operation	Digitalis 5 gr.	-	-	-	-
52	F	Sclerosis Thyroid	$\frac{185}{80}$	3 months	+	+	-	-	-	-	-

returned to distant homes and as their health was much improved in spite of the associated fibrillation they were never treated for it. In the more recent years such patients have been more systematically treated with quinidine and in about 85 per cent of them normal sinus rhythm has been restored. However, in spite of the absence of proper treatment, one notes certain suggestive points of difference among the cases of the three toxic groups outlined in Tables II, III, and IV. Auricular fibrillation in the diffuse parenchymatous or Graves' disease group tends to persist unless sinus rhythm is restored by means of quinidine, the diffuse adenomatous type, however, restoration of sinus rhythm followed operation alone 6 times in 10 cases. In the toxic nodular group it has existed usually for a longer period of time when the patient is first seen; it is apt to be more persistent and, if broken by quinidine, it is quite apt to relapse. Again, that fibrillation from thyrotoxicosis is not dependent upon degenerative changes of advancing years is suggested by its presence 5 times under the age of forty and 3 times under the age of thirty without the association of other heart diseases. That fibrillation and cardiac enlargement or congestive failure as well may exist at the age of 23, 25 or 29 without the aid of other cardiac disease is of much greater significance than the fact that they occur more frequently at an age when syphilis, cardiorenal hypertensive disease and the cardioscleroses are taking their greatest toll.

TREATMENT

The treatment of the goiter patient with thyroid heart disease has become, in our hands, more or less standardized. The patient, with or without auricular fibrillation, but without cardiac failure, is placed at bed rest for several days before operation. His diet contains from 45 to 55 grams of protein, from 1 to 2 grams of salt, calories as desired, and a fluid intake of 1000 to 1500 c.c. per day. Deodorized tincture of opium, minims 10, in capsules, is given from 2 to 6 times per day until he rests quietly. Opium given in this manner affords much comfort to the patient suffering from its influence. Iodine as a rule is given only to patients suffering from Graves' disease. Usually 5 minims of Lugol's solution three times per day for a few days before operation is sufficient to control the toxemia, but in the presence of a severe crisis it is given in large doses intravenously as sodium iodide, Lugol's solution by rectum and later by mouth until the acute thyrotoxic symptoms have subsided. After operation Lugol's solution, 5 minims a day, is often continued in these cases for 4 to 6 weeks. No special therapy is prescribed. The patient is directed not to exert himself to the point of shortness of breath for six months. In the presence of cardiac failure the problem is different. An attempt to restore compensation is made before operation is performed.

TABLE III
AURICULAR FIBRILLATION IN TOXIC DIFFUSE GOITER, PARENCHYMATOUS TYPE, 11 CASES

END-RESULTS

AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	RELIEVED BY			RELAPSED	PERMA- NENT	REMARKS
						OPERATION	STRO- PHANTHIN DIGITALIS	QUINIDINE SULPHATE			
25	F	Thyroid	$\frac{140}{70}$	2 years	+	-	-	-	-	+	-
38	F	Thyroid	$\frac{140}{80}$	5 months	+	-	-	-	-	+	-
55	M	Thyroid	$\frac{140}{80}$	6 months	+	+	-	-	-	-	-
29	F	Thyroid	$\frac{150}{90}$	6 months	+	+	-	-	-	-	-
40	F	Thyroid	$\frac{122}{78}$	5 months	+	-	-	-	-	+	-
42	F	Thyroid	$\frac{160}{80}$	6 months	+	-	-	-	-	+	-
44	F	Thyroid	$\frac{158}{90}$	10 years	+	-	-	-	-	+	-
37	M	Thyroid	120	6 months	+	-	-	-	-	+	-
54	F	Thyroid		5 years	+	-	-	-	-	+	Died before opera- tion
55	M	Sclerosis Thyroid	$\frac{185}{85}$	2 years	-	Followed operation	-	48 grains 21 grains 6 grains	+		Died 1 year later. Cerebral hemor- rhage
50	F	Thyroid	$\frac{140}{80}$	2 years	+	-	-	-	-	+	-

TABLE IV
TOXIC NODULAR GOTTER, 18 CASES

AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	RELIEVED BY			PERMA- NENT	REMARKS
						OPERATION	STRO- PHANTHIN DIGITALIS	QUINIDINE SULPHATE		
61	F	Sclerosis Thyroid		Paroxysmal	+	-	-	-	-	-
56	F	Thyroid	$\frac{105}{60}$	Paroxysmal	-	-	-	-	-	-
52	F	Thyroid	$\frac{156}{90}$?	-	-	Digitalis	-	-	-
55	F	Thyroid	$\frac{180}{90}$?	-	-	-	-	-	-
62	F	Sclerosis Thyroid	$\frac{120}{80}$?	+	-	-	61 grains	-	-
53	F	Sclerosis Thyroid	$\frac{166}{92}$?	-	-	-	-	-	-
41	M	Thyroid	$\frac{170}{80}$?	-	-	-	-	-	-
52	F	Sclerosis Thyroid	$\frac{220}{120}$?	-	-	Quinidine	+	-	-
58	F	Sclerosis Thyroid	$\frac{190}{90}$	Paroxysmal	-	-	-	-	-	-
					-	Strophan- thin	-	-	+	-
					-	-	-	-	-	Precipitated by operation

TABLE IV CONTINUED

END-RESULTS

AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	RELIEVED BY			RELAPSED	PERMA- NENT	REMARKS
						OPERATION	STRO- PHANTHIN DIGITALIS	QUINIDINE SULPHATE			
62	F	Sclerosis Thyroid	$\frac{160}{90}$?	+	-	-	-	-	+	-
60	F	Sclerosis Thyroid	$\frac{250}{120}$?	+	-	-	-	-	+	-
53	F	Sclerosis Thyroid	$\frac{165}{90}$?	+	-	-	-	-	+	-
48	F	Thyroid	$\frac{170}{75}$?	+	-	-	-	-	+	-
59	F	Sclerosis Thyroid	$\frac{145}{80}$?	-	-	-	-	-	+	Began 3 years after operation 126 grains Quinidine--no result
63	F	Sclerosis Thyroid	$\frac{170}{80}$	10 years ago relieved by operation 5 months	+	-	-	-	-	+	-
50	F	Sclerosis Thyroid	$\frac{165}{90}$	4 years	+	-	-	-	-	+	-
46	F	Thyroid	$\frac{170}{85}$	1 year	+	-	-	-	-	+	-
52	F	Sclerosis Thyroid	$\frac{180}{90}$	9 months	+	-	-	-	-	+	-

In a limited number of cases it has been impossible to overcome the failure, and, after careful consideration of each case, thyroidectomy has been done in its presence. This course has been followed in only a few instances, and fortunately, thus far, without an immediate operative death. With the presence of general edema treatment is often started with a Karell milk diet, and after two days of its use the diet is changed to the above low protein, low salt diet, and the liquid intake restricted to 800 c.c. or less per day. The Minnesota grown powdered digitalis leaves are administered, 4 grains per day, until physiological tolerance is reached. Complete digitalization is usually obtained in three to five days. At times strophanthin, gr. 1/500 (B. & W.) intravenously administered, and repeated in two hours, is used at the beginning of treatment. This is given particularly in the presence of severe congestive symptoms and rapid fibrillation. Salyrgan is a valuable adjunct in the removal of fluid from the body. After compensation is restored and the patient has become quiet, all digitalis is stopped for a period of three or four days—following the idea of Plummer that the operative risk is less after the patient is out from under its influence. We have no evidence to substantiate this idea. After operation a long period of control of the heart is enjoined upon the patient. He is urged

TABLE V

RÉSUMÉ OF AURICULAR FIBRILLATION IN DIFFUSE AND NODULAR GOITER

Group I.—

1. Diffuse goiter, toxic

(a) Diffuse parenchymatous (exophthalmic) 11 cases

Average age 42.6 years (25 to 55 years)

Sex: Male 3, Female 8

Cardiac pathology: Thyroid heart 11, with cardiosclerosis 1

Average blood pressure: Systolic 145.5 millimeters of mercury

Diastolic 81.4 millimeters of mercury

Duration: usually a few months

End-result: usually permanent unless treated with quinidine

(b) Diffuse adenomatous (disseminated or spotty parenchymatous)

Goiter: 10 cases

Average age 48.5 years (23-62 years)

Sex: Male 2, Female 8

Cardiac pathology: Thyroid heart 10 Cardiosclerosis 6

Average blood pressure: Systolic 170 millimeters of mercury

Diastolic 88 millimeters of mercury

Duration: usually few months

End-result: sinus rhythm seemingly more easily restored

2. Diffuse goiter, nontoxic, no cases

Group II.—

1. Nodular Goiter, toxic, 18 cases

Average age 54.5 years (41 to 63 years)

Sex: Male 1, Female 17

Cardiac pathology: Thyroid heart 18 Cardiosclerosis 12

Average blood pressure: Systolic 145.5 millimeters of mercury

Diastolic 84.4 millimeters of mercury

Duration: usually long continued

End-result: usually permanent or relapsing

2. Nodular goiter: nontoxic, no cases

to live quietly without exertion for a period of a year. Many times this advice is not followed. Sometimes the patient returns after a few weeks or months again in failure and it is then that recompensation is obtained with the greatest difficulty; in fact many times it is not obtained. The favorable prognosis for failure seen before and with thyroidectomy becomes the gloomy prognosis of failure seen in the syphilitic and the cardiorenal heart. Associated heart lesions often play a role in the return of failure, but in some of our patients they have not played such a role.

The frequent presence of auricular fibrillation in thyroid heart disease adds an interesting phase to the treatment of the thyrotoxic patient. Formerly when quinidine sulphate was used with considerable apprehension the patient with persistent fibrillation was directed to return from 4 to 6 weeks after operation for its administration. As experience in its use was gained, however, we gave it to patients with less and less delay, until for the past two years we have given an initial test dose of 3 grains on the third and fourth days after operation. Then, without untoward symptoms appearing, we have administered 3, 6 and 9 grains per dose three times per day until sinus rhythm was restored or failed to be obtained. No two patients respond alike. Amounts of quinidine administered have ranged from the initial dose of 3 grains to 500 grains during one period of treatment. One or two grains per day are often prescribed for a week or longer after normal sinus rhythm has been resumed, in the hope of preventing recurrence of fibrillation. Should recurrence take place quinidine is again given. Thus far we have seen no accidents attend its use, and we have learned to look upon the procedure as safe when carried out under control. When auricular fibrillation remains persistent it is often necessary to control it by suitable tonic doses of digitalis, for fibrillation occurring with the thyroid heart tends to be of rapid rate and cause symptoms of embarrassed heart action by reason of its rapidity.

SUMMARY

Eight hundred and thirty-five goiter cases from the Pacific Northwest states are analyzed, chiefly from the standpoint of cardiac enlargement, cardiac failure, and auricular fibrillation in relation to age incidence, basal metabolism, arterial hypertension, associated cardiopathies and the type of the goiter present.

Although cardiac failure and auricular fibrillation are seen usually as an accompaniment of advancing years, it is pointed out that they occur also before the age of thirty in goiter patients in whom other heart diseases are absent. This fact, together with the characteristic thyrogenic heart action and certain experimental evidence, suggests the probability of specific thyroid heart lesions.

The general plan of treating heart complications in thyrotoxicosis in the clinic is outlined.

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CARDIOVASCULAR SYMPTOMATOLOGY IN EXOPHTHALMIC GOITER*

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IN THE past two and a half years the histories and physical examinations of patients coming to the Thyroid Clinic have been recorded on a special record sheet. This is designed to permit the use of modern mechanical methods to analyze the data. The method of recording the information, the transfer to punch cards, and its analysis by means of a sorting machine have been described elsewhere.¹ By the use of these methods, we have now available information on 619 patients with goiter seen from January, 1930, to February, 1932, inclusive. Those with a questionable diagnosis were excluded. The present study is based on an analysis of 184 cases of toxic goiter, using 233 cases of non-toxic nodular goiter as control. The toxic group contains cases of nodular goiter with hyperthyroidism as well as cases of exophthalmic goiter. The tables have been arranged to bring out differences in symptomatology in the two sexes occurring in hyperthyroidism. The control group, however, has not been subdivided because the 18 male patients belonging to this group are not sufficient for a control. Consequently the group of non-toxic nodular goiter is adequate as a control only for the female patients with hyperthyroidism.

TABLE I

AGE DISTRIBUTION OF 233 PATIENTS WITH NON-TOXIC NODULAR GOITER AND OF 184 PATIENTS WITH TOXIC GOITER

AGE	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
-19	18	7.7	3	5.8	13	9.8
20-29	37	15.9	10	19.2	33	25.0
30-39	72	30.9	9	17.3	34	25.8
40-49	54	23.2	19	36.5	32	24.2
50-59	42	18.1	8	15.3	15	11.4
60-69	7	3.0	3	5.8	5	3.8
70+	3	1.3				
Total	233		52		132	

*From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital.

RESULTS

Table I gives the age distribution of patients with hyperthyroidism, 52 males and 132 females, and of 233 patients with non-toxic nodular goiter. It is seen that male hyperthyroid patients were older than females to some extent. Thus 25 per cent of the male patients belonged in the age group under thirty years and 21.1 per cent in the group of fifty years and over. The corresponding figures for female patients are 34.8 per cent and 15.2 per cent respectively. The ages of the non-toxic goiter group were about the same as those of the male hyperthyroid group.

TABLE II
THE BASAL METABOLIC RATE IN NON-TOXIC NODULAR GOITER AND IN HYPERTHYROIDISM

	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
-Minus 20	4	1.7				
Minus 19-Minus 10	29	12.5				
Minus 9-Minus 1	61	26.1				
0-Plus 14	114	48.9	2	3.8	7	5.3
Plus 15-Plus 29	25	10.7	6	11.5	34	26.0
Plus 30-Plus 44			22	42.3	49	37.4
Plus 45-Plus 59			10	19.2	28	21.4
Plus 60-Plus 74			10	19.2	9	6.9
Plus 75+			2	3.8	4	3.1

Table II shows the comparison of severity of hyperthyroidism as measured by the basal metabolic rate in male and female patients. On the whole, there were more severe cases among the males than among the females. Thus 23 per cent of the male patients had metabolic rates of plus 60 and over, whereas only 10 per cent of the female patients had this degree of metabolism.

In Table III the important cardiac symptoms are analyzed with respect to their frequency, severity and duration. In general all of the symptoms were more common in the female than in the male patients with hyperthyroidism, in spite of the fact that the male patients were older and more frequently had a severe form of the disease. The actual correction for age and basal metabolic rate makes a slight change only in the percentage figures. For example, the incidence of palpitation in male hyperthyroid patients changes from 77.0 to 75.3 per cent and for

females it changes from 91.7 to 92.6 per cent. It is interesting to note that the frequency of precordial pain in hyperthyroidism is not much greater than in the control group.

This table, in addition, shows that the severity of the cardiac complaints was greater in the hyperthyroid than in the non-toxic patients and that the symptoms were much milder in the male than in the female

TABLE III

THE INCIDENCE OF SOME IMPORTANT CARDIAC SYMPTOMS, AND OF THEIR SEVERITY AND DURATION IN NON-TOXIC NODULAR GOITER AND IN HYPERTHYROIDISM

	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Palpitation	119	51.1	40	77.0	121	91.7
Irregular heart	11	4.8	4	7.7	12	9.2
Dyspnea	115	49.6	39	75.0	117	88.6
Precordial pain	36	15.8	7	13.7	26	20.2
Average severity:						
Mild	107	73.8	26	55.3	42	33.3
Moderate	36	24.8	18	38.3	68	54.0
Severe	2	1.4	3	6.4	16	12.7
Duration:						
-1 month	1	0.7	2	4.3	2	1.6
1-4 months	13	9.0	10	21.3	25	19.8
4-12 months	19	13.1	15	31.9	36	28.6
1-2 years	27	18.6	12	25.5	15	11.9
2-5 years	35	24.1	4	8.5	34	27.0
5-10 years	18	12.4	1	2.1	6	4.8
10+ years	12	8.3	2	4.3	7	5.6
Unknown	20	13.8	1	2.1	1	0.8

patients. The duration of cardiac symptoms was longer in the non-toxic than in the toxic groups, and longer in the female than in the male group. For example, 20.7 per cent of the patients with non-toxic goiters had cardiac symptoms for 5 years or longer, whereas 10.4 per cent of the female and 6.4 per cent of the male patients with hyperthyroidism had symptoms of this duration. The percentage of patients having symp-

toms for less than 4 months was 9.7 per cent, 21.4 per cent and 25.6 per cent respectively.

Table IV shows the incidence of a variety of symptoms and signs dealing with the cardiovascular system or having some bearing on it. Several important facts may be deduced. Female hyperthyroid patients tended to be heavier than male patients; they had exophthalmos less

TABLE IV

THE INCIDENCE OF MISCELLANEOUS CARDIAC SYMPTOMS AND SIGNS IN NON-TOXIC NODULAR GOITER AND IN HYPERTHYROIDISM

	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Increased heat loss*	60	25.9	45	86.6	116	87.8
Weakness	139	60.0	41	78.8	115	88.5
Obesity	45	19.3	-	-	7	5.3
Underweight	41	17.6	25	48.1	57	43.2
Exophthalmos	4	1.8	36	70.6	73	53.8
Cyanosis of lips	2	0.9	2	3.8	4	3.0
Pallor of lips	16	6.9	-	-	4	3.0
Thyroid:						
Normal	2	0.9	4	7.7	5	3.8
Slightly enlarged	147	63.1	35	67.3	83	62.9
Moderately enlarged	76	32.6	13	25.0	44	33.3
Greatly enlarged	8	3.4	-	-	-	-
Cardiac enlargement	23	9.9	15	28.9	55	42.3
Fibrillation	2	0.9	6	11.5	9	6.8
Other arrhythmias	6	2.6	3	5.8	5	3.8
Orthopnea	7	3.0	5	9.6	10	7.6
Precordial thrill	2	0.9	3	5.8	12	9.2
Valvular disease	3	1.3	1	2.0	4	3.1
Pericardial disturbance	-	-	3	5.9	15	11.8
Arteriosclerosis-peripheral	69	29.6	32	61.6	26	19.7
Cardiac disease	30	12.9	7	13.5	17	12.9
Cardiac disease without rheumatic heart disease	26	11.2	6	11.5	15	11.4

*Includes symptoms of increased sensation of heat and increased perspiration.

often, and their goiters tended to be larger. Cardiac enlargement, as measured by percussion, was more common in the female, whereas auricular fibrillation and other forms of arrhythmia were more common in the male. The cardiac enlargement is more often apparent than real, because the size of the heart, as obtained by percussion, is exaggerated by its overactivity and very often does not check with the measurements obtained by roentgen ray. A precordial thrill was felt more frequently in the female than in the male patient. Valvular disease occurred in the control to almost the same extent as in the hyperthyroid groups. Evidence of pericardial disturbance in the form of a friction rub, to be discussed below, was more common in the female. Of the above factors, cardiac enlargement, precordial thrill and pericardial friction rub are partly indicators of the degree of activity of the heart.

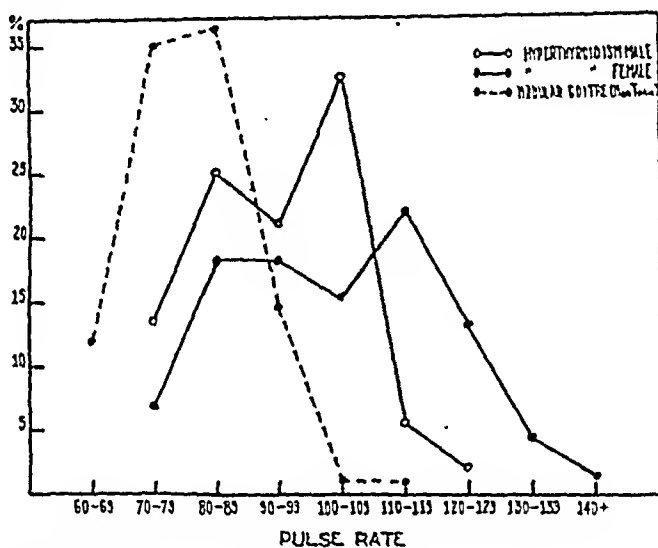


Fig. 1.—Distribution of the pulse rate in 51 male patients with hyperthyroidism, 131 female patients with hyperthyroidism and 233 patients with non-toxic nodular goiter.

It seems, therefore, that the heart was more overactive in the female than in the male hyperthyroid patient.

The incidence of peripheral arteriosclerosis in the female hyperthyroid group, namely 19.7 per cent, was to be expected on the basis of age distribution, using the control group of non-toxic nodular goiters for comparison. The incidence of peripheral arteriosclerosis in the male toxic goiter group was about three times that of the female group. Since the control group was composed mainly of female patients, it is impossible to say whether the high incidence of arteriosclerosis in the male group was abnormal or to be expected on the basis of age. It is possible that male patients have their disease for a much longer period of time than the results indicate, since notoriously they complain very little until late in the course. Consequently the changes in the vessels, resulting from long standing thyrotoxicosis may account for part of the large number with

arteriosclerosis. The incidence of organic cardiac disease was about the same in the three groups of patients, i. e., 13 per cent.

The relation of pulse rate to pulse pressure in hyperthyroidism showed interesting difference between the sexes. The pulse in male patients was slower than in female patients, as indicated in Fig. 1. For example, 38.5 per cent of the males showed pulse rates under 90, against 25.2 per cent of females, and 7.7 per cent of males showed pulse rates of 110 and over against 41.2 per cent of females. This difference in pulse rates existed in spite of the greater number of severe cases in the male group. In terms of averages and their standard deviations, this difference may be expressed 104.0 ± 1.5 — 94.8 ± 1.7 or 9.2 ± 2.5 , a value of high statistical significance. On the other hand the pulse pressure of the male group was larger than that of the female (Fig. 2). For example,

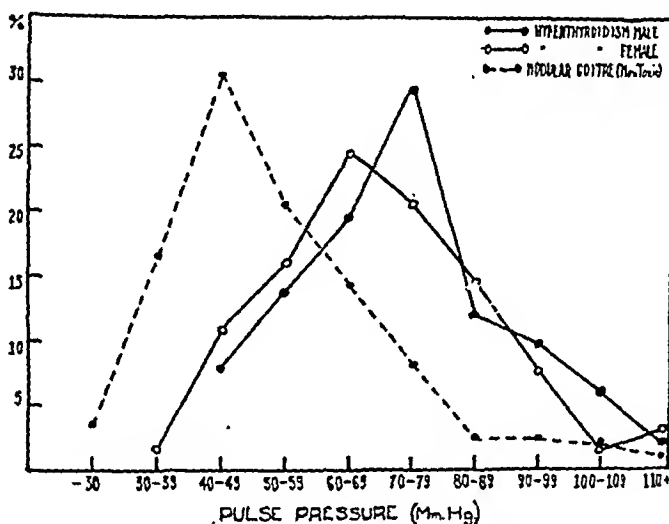


Fig. 2.—Distribution of the pulse pressure in 51 male patients with hyperthyroidism, 131 female patients with hyperthyroidism and 226 patients with non-toxic nodular goiter.

21.4 per cent of the male patients had pulse pressures under 60 mm. of Hg against 28.2 per cent of the female patients; 17.7 per cent of the male patients had pulse pressures of 90 mm. and over, against 12.2 per cent of the females. This difference as expressed by averages is 74.0 ± 2.3 — 70.0 ± 1.5 or 4.0 ± 2.9 , a value of probable significance, although not of the same order as in the case of the pulse rate because of the greater dispersion of readings. Since the pulse pressure is roughly an indication of the output of the heart per beat, it seems that the net result as far as the volume flow of blood is concerned was the same in the two groups. In the one the demands upon the circulation were largely met by increasing the heart rate and in the other by increasing the output per heart beat.

The attempt has been made to correlate the important cardiac symptoms of palpitation and dyspnea and their severity with some of the fac-

TABLE V

THE CORRELATION OF PALPITATION AND DYSPNEA IN HYPERTHYROIDISM AND THEIR SEVERITY WITH SOME RELATED FACTORS (PERCENTAGE FREQUENCY)

	PALPITA- TION	DYSPNEA	SEVERITY OF PALPITATION AND DYSPNEA		
			MILD	MODERATE	SEVERE
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
<i>Average Frequency</i>	87.5	84.8	39.3	49.7	11.0
Obesity	100.0	100.0	14.4	85.6	-
Undernourishment	92.7	86.6	35.4	50.6	14.0
Size of thyroid:					
1. Normal	88.9	100.0	55.5	33.5	11.0
2. Slight enlargement	85.6	82.2	37.6	51.4	11.0
3. Moderate enlarge- ment	91.2	87.7	40.0	49.2	10.8
Cardiac enlargement	95.7	87.2	21.7	59.4	18.9
Fibrillation	100.0	100.0	26.6	40.0	33.3
Other arrhythmias	100.0	87.5	25.0	75.0	-
Preordial thrill	100.0	93.3	20.0	66.7	13.3
Valvular disease	100.0	100.0	-	60.1	39.9
Pericardial disturbance	88.9	88.9	27.8	66.6	5.6
Arteriosclerosis-pe- ripheral	86.2	82.8	45.5	43.6	10.9
Cardiac disease	95.8	95.8	23.8	47.6	28.6
Basal metabolic rate:					
Under 30	79.6	75.5	41.5	51.2	7.3
30-44	87.3	87.3	43.5	44.9	11.6
45+	93.6	88.9	33.9	54.8	11.3
Pulse rate:					
Under 100	84.1	84.1	48.8	41.5	9.7
100+	90.5	85.3	31.1	57.8	11.1
Pulse pressure:					
Under 80	83.3	84.1	41.8	48.4	9.8
80+	100.0	87.0	32.0	54.0	14.0

tors mentioned above. They are listed in Table V. The incidence of palpitation and dyspnea in all the hyperthyroid patients was 87.5 per cent and 84.8 per cent respectively, and of their severity 39.9 per cent, 49.7 per cent and 11.0 per cent for mild, moderate and severe degree respectively. Age did not affect the frequency of these two symptoms except for the small group of patients under 20 years for which the incidence was 62.5 per cent for each symptom. The severity did not show a consistent trend with age, but there was a slight tendency to greater severity in the older age groups. Both obesity and undernourishment were associated with a greater frequency of palpitation and dyspnea and a greater severity than usual. The size of the thyroid gland did not show a consistent relationship. There was a greater than average incidence of palpitation and dyspnea, as well as greater severity, in the groups of patients with cardiac enlargement, fibrillation, other arrhythmias, precordial thrill, valvular disease, other organic cardiac disease, and pericardial friction rub. On the other hand peripheral arteriosclerosis was not associated with such an increase. There was a direct correlation between the incidence of palpitation and dyspnea and their severity on the one hand, and the level of metabolism, pulse rate and pulse pressure on the other, with the exception of dyspnea in relation to the pulse rate. The relationship between the severity of symptoms and the metabolism was somewhat dubious. Some of the factors associated with a high incidence of palpitation and dyspnea and with greater than average severity were more frequent in the male, and some in the female. The variation was such that it is impossible to account on this basis for the greater frequency of palpitation and dyspnea in the female and also for the greater severity of these symptoms.

As indicated previously, there were 24 patients with organic cardiac disease associated with hyperthyroidism. Three of these had rheumatic heart disease. In Table VI is listed the incidence of various symptoms and signs in this group. All but one of these patients were 40 years of age or older. Compared to the group uncomplicated by cardiac disease, the incidence of palpitation and dyspnea was greater by about 10 per cent. There was more obesity, and the goiters tended to be smaller. Cardiac enlargement was present to the extent of 86 per cent, against 32 per cent for the uncomplicated group, fibrillation 57 per cent, against 1.8 per cent, other arrhythmias 14 per cent, against 3 per cent, and peripheral arteriosclerosis 71 per cent, against 27 per cent. Precordial thrill, valvular disease and pericardial disturbance were less common in the group with cardiac disease. Finally, the basal metabolic rate, the pulse rate and pulse pressure varied little from those of the uncomplicated group.

DISCUSSION

The supposition of a special toxic damage to the cardiovascular system in hyperthyroidism has been made by many. There is one im-

portant difference between the non-toxic and the toxic groups. In the former, cardiac disease took the form of hypertensive or arteriosclerotic heart disease in 20 of the 30 cases, auricular fibrillation in 1, paroxysmal tachycardia in 2, and angina in 1; in the latter, cardiac disease took the form of hypertensive and arteriosclerotic heart disease in 5 of the 24

TABLE VI

INCIDENCE OF CERTAIN SYMPTOMS AND SIGNS PRESENT IN 21 PATIENTS WITH CARDIAC DISEASE ASSOCIATED WITH HYPERTHYROIDISM COMPARED TO THAT SEEN IN UNCOMPLICATED CASES OF HYPERTHYROIDISM

	CARDIOVASCULAR GROUP		UNCOMPLICATED GROUP	
	NO.	PER CENT	NO.	PER CENT
Palpitation	20	95.2	141	86.5
Dyspnea	20	95.2	136	83.4
Obesity	2	9.5	5	3.1
Undernourishment	9	42.8	73	44.8
Size of thyroid:				
Normal	3	14.3	6	3.7
Slight enlargement	14	66.7	104	63.8
Moderate enlargement	4	19.1	53	32.5
Cardiac enlargement	18	85.7	52	32.3
Fibrillation	12	57.1	3	1.8
Other arrhythmias	3	14.3	5	3.1
Precordial thrill	1	4.8	14	8.6
Valvular disease	0	0	5	3.1
Pericardial disturbance	0	0	18	11.5
Arteriosclerosis-peripheral	15	71.4	43	26.8

cases, and of either auricular fibrillation, angina or congestive failure, singly and in combination, in 16 cases. It seems, therefore, that in the hyperthyroid group cardiovascular damage consists chiefly in a functional disturbance rather than a structural change. The fact that almost all these people were older than the hyperthyroid patients without cardiac disease, and the high incidence of peripheral arteriosclerosis suggest that hyperthyroidism *per se* is not responsible for the so-called thyroid heart disease, but produces functional disturbance in a previously damaged cardiovascular system. This surmise is supported by the fact that we often see patients who have had hyperthyroidism for ten years or more without any evidence of cardiac damage. It is, never-

theless, true that occasionally a young person with thyrotoxicosis develops cardiac failure without evidence of a previously damaged heart. The above findings are in agreement with the conclusions of Andrus.²

As mentioned earlier, we have noted an unusual systolic noise in the moderate and severe cases of hyperthyroidism. It consists of a rough, grating systolic murmur which has some of the characteristics of a friction rub, heard best over the sternum in the region of the second interspace. It is superficial, heard best at the end of full expiration and obscured by full inspiration. Its intensity subsides as the metabolism and heart rate drop under the influence of iodine and usually disappears after operation. On several occasions the diagnosis of pericarditis was suspected by members of the hospital staff on the basis of this friction rub. We are not certain as to its causation. The fact that it is superficial and disappears with inspiration has led us to believe that it is pleuro-pericardial in origin. It may have some relationship to the dilated pulmonary conus often seen in the roentgen ray pictures in this condition. In the above series a superficial friction rub was observed in 10 per cent of the patients, but this figure represents only the outspoken cases. The milder friction sounds were not recorded. At present no diagnostic or prognostic significance can be attached to it.

Some time after we became aware of the existence of this sign, we found that other observers had described it in the literature. Goodall³ in 1920 noted a superficial pericardial rub in patients with hyperthyroidism, most common over the pulmonary area and often associated with a definite cardiac oppression or actual pain. He suggested that it was probably produced mechanically by a dilated heart. In 1927 Smith and Calvin⁴ also described a systolic rubbing sound in the pulmonic area in 40 or 50 per cent of their patients. In some it was very intense; in others it seemed to roughen the systolic murmur already present in this area.

SUMMARY

An analysis of 184 patients with hyperthyroidism shows that cardiac symptoms are more common in the female; their severity is greater and their duration longer. Cardiac enlargement, precordial thrill and a superficial pericardial friction rub are more common in the female, whereas auricular fibrillation and other forms of arrhythmia are more common in the male. Cardiovascular disease is present in the male and female patients to the same degree.

The pulse rate tends to be slower in the male than in the female, while the pulse pressure is higher. It may be inferred, therefore, that the increased volume flow of blood is about the same in the two groups, although brought about by different mechanisms.

Various factors influence the frequency of palpitation and dyspnea and their severity.

Twenty-one patients with organic cardiac disease are analyzed. It is indicated that hyperthyroidism *per se* does not produce so-called thyroid heart disease but causes functional derangement in a cardiovascular system already damaged by other pathological conditions.

A superficial pleuro-pericardial friction rub heard over the sternum is described.

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(For discussion, see page 144.)

THE HEART IN HYPERTHYROIDISM: A CLINICAL AND EXPERIMENTAL STUDY*†

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THE cardiac manifestations of hyperthyroidism constitute a most prominent phase in this syndrome. Yet it is often difficult, sometimes impossible, to correlate the severity of these with the other clinical signs. At one extreme, signs of cardiac failure may be so conspicuous as to mask the concomitant hyperthyroidism. At the other, a patient may perish in the flame of a "thyroid crisis" without symptoms of myocardial insufficiency.

Tachycardia is frequently an early, and often a prominent, manifestation of the disease. Even more characteristic is the lability of the heart rate, such that it reflects exertion, excitement, emotion and fatigue to an unusual degree. Sooner or later, in nearly every case, this engenders "palpitation," which may vary in severity from an unusual awareness of the heart beat on the part of the patient during and following exertion to a most distressing, thumping, pounding sensation, which annoys the patient even at rest and renders exertion unbearable.

The blood pressure, like the heart rate, in such patients undergoes sudden and conspicuous variations. The studies of Fullerton and Harrop³ indicate that, under basal conditions, neither the maximum pressure nor the pulse pressure is abnormal. During emotion or excitement the pulse pressure may greatly increase so that a systolic-diastolic difference of 80-100 mm. Hg is no uncommon finding. In the absence of coexistent vascular disease the diastolic pressure is rarely raised, indeed it may often be lowered; the systolic pressure is frequently elevated.

Both of these mechanisms (tachycardia and high pulse pressure) contribute to the increased circulatory minute-volume characteristic of any condition which augments the rate of metabolism.

The precordial impulse is diffuse, rapid and forceful. The apex impulse is frequently slapping; the sharp shock of closure of the pulmonary valves is often palpable. The relative cardiac dullness is sometimes demonstrably enlarged; particularly common is an enlargement to the left in the third and fourth interspaces. The heart sounds are loud and sharp; the first sound at the apex and the pulmonary second sound are often accentuated. Blowing systolic murmurs are frequently

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When read before the Annual Meeting of the American Heart Association, New Orleans, May 10, 1932, this paper was presented in two parts, "The Cardiac Manifestations of Hyperthyroidism" and "Experimental Observations Upon Hearts of Thyroxinized Animals."

†The expenses of this study were defrayed in part by the Bingham Fund of the Johns Hopkins University.

audible in the mitral and pulmonic areas. Fluoroscopy often reveals the enlargement of the cardiac shadow, particularly of the second curve to the left; especially striking is the visibly great amplitude of contraction of the ventricles.

It is a significant fact that none of these symptoms or signs are peculiar to hyperthyroidism. The diagnosis of what has been termed "thyroid-heart" is finally made, in the majority of instances, by demonstrating anatomical or functional abnormalities in the thyroid gland rather than in the heart. Particular importance attaches to the cardiovascular symptoms and signs for the reason that, in a certain proportion of cases, myocardial insufficiency supervenes. That, however, signs of congestive heart failure are often absent in what appear to be the most severe instances of the disease constitutes a perplexing phase of this clinical problem.

The present report deals with 200 cases of hyperthyroidism followed in the Johns Hopkins Hospital. All were carefully studied upon the medical wards, and after a suitable period of medical treatment, were subjected to subtotal thyroidectomy. The majority of cases returned to the medical wards for a period of postoperative observation.

According to the pathologist's report upon the portion of the thyroid gland removed, the cases were divided into two groups: exophthalmic goiter and adenomatous goiter with hyperthyroidism.

TABLE I.

	EXOPHTHALMIC GOITER	ADENOMATOUS GOITER
Total cases	158	42
Cases with cardiac failure	23	14
Average age	34.7 yr.	45.3 yr.
Average B.M.R.	+50.6	+42.6
Average duration of symptoms	12.6 mo.	22.4 mo.

Table I contrasts certain data concerning the two types. It is not our purpose to enter here into a discussion of the difference between exophthalmic goiter and "toxic adenoma." Suffice it to point out the greater age and duration of symptoms in the cases of nodular goiter. That these factors appear to combine to affect the reaction of the heart to this disease is indicated by the incidence of myocardial insufficiency in the two groups. Among 158 cases of exophthalmic goiter 23 or 14.55 per cent showed signs of congestive heart failure upon entering the hospital. The 42 cases of adenomatous goiter, on the other hand, included 14 (33 $\frac{1}{3}$ per cent) with myocardial insufficiency.

In Chart 1 the incidence of congestive heart failure is related to the duration of symptoms.

Among all the cases of exophthalmic goiter in this series the average duration of symptoms of hyperthyroidism was 12.6 months. In those without cardiac failure it was eleven months, and in those with failure

the average duration of symptoms was 21+ months. In the group of what we have classified as adenomatous goiter there was usually a history of symptoms of hyperthyroidism for many months, often of goiter for years, and not infrequently a story of one or more previous attacks.

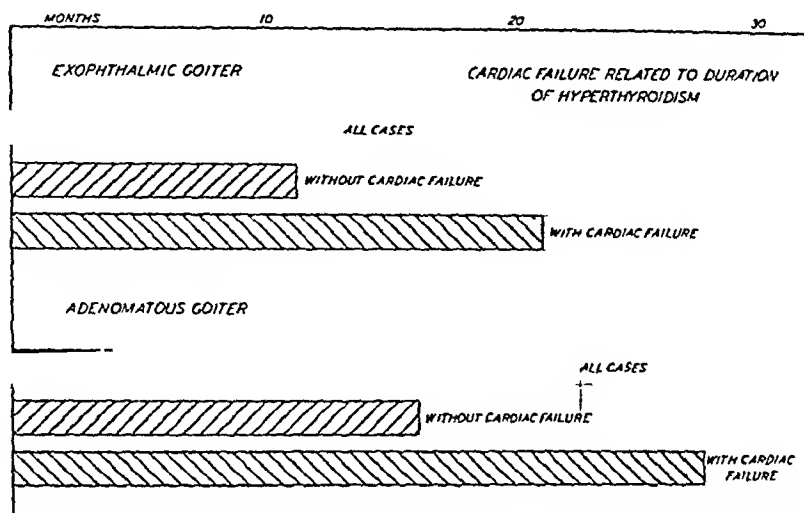


Chart 1.—Cardiac failure related to duration of symptoms among 200 cases of hyperthyroidism.

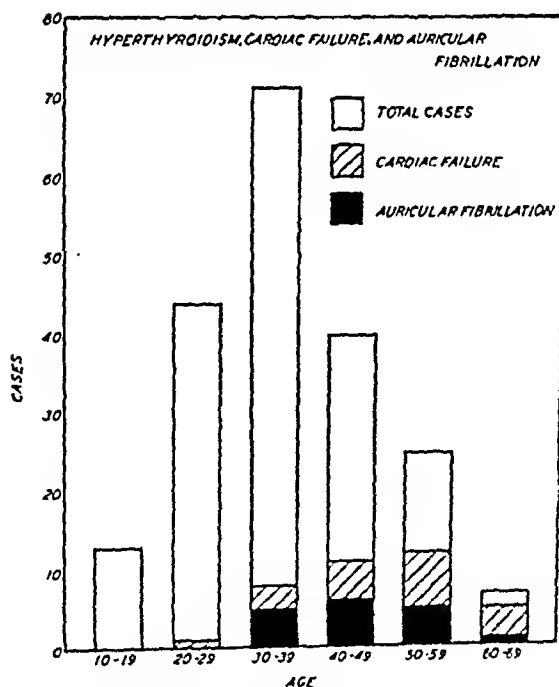


Chart 2.—Incidence of cardiac failure and auricular fibrillation among 200 cases of hyperthyroidism.

Here the average duration of symptoms was greater than in the first group: all cases, 22.4 months; with failure, twenty-eight months; without failure, sixteen months.

In Chart 2 is shown the occurrence of cardiac failure in this series. Each age decade above 30 includes a larger proportion of cases with

myocardial insufficiency; the incidence becomes conspicuously greater among those over forty years of age. This is to be ascribed to the natural diminution of the cardiac reserve which takes place with the years beyond forty and to the coincidence of organic—hypertensive, arteriosclerotic or rheumatic—cardiac disease with hyperthyroidism among the older patients in this series.

Among 112 cases of exophthalmic goiter and 16 cases of adenomatous goiter with hyperthyroidism under forty years of age, only nine showed signs of myocardial insufficiency. In five of these physical signs of mitral stenosis and insufficiency were demonstrable after the metabolic rate had fallen to normal. A sixth patient died; in this instance Aschoff bodies were demonstrated in the myocardium. Another patient, a young negroess of twenty-six, who developed myocardial insufficiency with hyperthyroidism of only nine months' duration, had a positive Wassermann and signs of syphilis of the aorta. Thus, in 7 of these 9 cases there was found what was taken to be evidence of coexistent heart disease. All have been examined from twelve to eighteen months after discharge. The signs of organic cardiac disease persist.

Chart 2 also indicates that, in this series, established auricular fibrillation was associated with myocardial insufficiency in 17 cases. Transient periods of auricular fibrillation not uncommonly occurred in these patients. Such paroxysmal irregularities of the cardiac rhythm are not always associated with cardiac failure and frequently fail to recur following surgical relief of hyperthyroidism. Established auricular fibrillation is a much graver complication. The consequently irregular ventricular rhythm, unless its rate can be controlled with digitalis, presents a serious handicap to an already overburdened circulation.

EXPERIMENTAL

A series of observations have been conducted in this laboratory to study the effects of thyroxine* upon the hearts of animals:

1. *Effect of Thyroxine and Desiodothyroxine in Vitro.*—In some experiments, previously reported by Lewis and McEachern,⁶ the auricles of normal rabbits were suspended in thoroughly oxygenated Ringer-Locke's solution in a Dale bath; in others the entire hearts of such animals were perfused with Ringer-Locke's solution by the Langendorff method. Thyroxine (Roche) added to the bath or to the perfusing solution produced no effect in concentrations up to 1/25,000. Desiodothyroxine (Harrington) was also without effect in concentrations up to 1/20,000. Such experiments were continued for as long as 8 hours during which the rate of the spontaneous rhythm gradually slowed; at no time was there any evidence of an augmenting action of thyroxine.

Recently Markowitz and Yater⁷ have reported that cardiac muscle, explanted from the embryo chick after the first 48 hours of incubation, and

*The author desires to acknowledge the cooperation of Hoffmann-LaRoche, Inc. in furnishing a portion of the thyroxine used in these experiments.

incubated in the presence of 1/50,000 thyroxine, developed and sustained a more rapid spontaneous rhythm than control fragments of the same hearts which had not been exposed to thyroxine. It is of interest to note that even such a large dose of thyroxine produced its effect only after 12 hours' contact with the cardiac tissue.

2. *Physiological Properties of the Hearts of Thyrotoxicized Animals.*—Attempts to reproduce Graves' disease in animals by the administration of thyroxine have not, to our knowledge, met with success. It is, however, possible by such means to reproduce that phase of the syndrome which is due to hyperthyroidism.

COMPARISON OF THE MAXIMUM RATES OF ISOLATED HEARTS (LANGENDORFF APPARATUS) AND ISOLATED AURICLES (DALE BATH) OF NORMAL AND THYROTOXIC RABBITS.

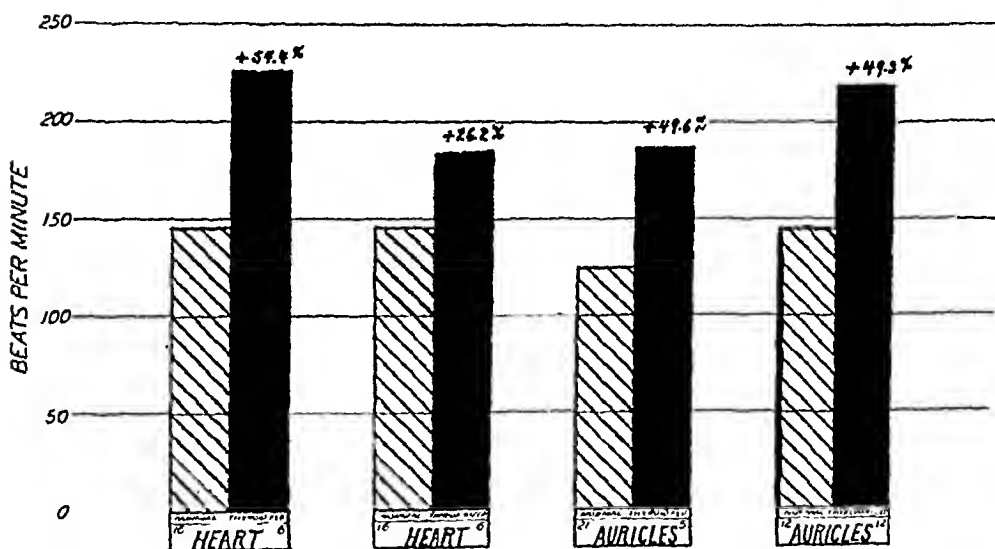


Chart 3.—Comparison of the maximum rates of isolated hearts (Langendorff apparatus) and isolated auricles (Dale bath) of normal and thyrotoxic rabbits.

If one injects into a rabbit 0.5 mg. thyroxine per kilogram body weight, events ensue which are homologous with the clinical signs of hyperthyroidism. During the first twenty-four hours after the injection no change may be noted. This "latent period" finds a clinical counterpart in the interval elapsing between the surgical removal of a portion of the thyroid gland from a patient with Graves' disease and the "postoperative storm" which not infrequently follows. By the end of 36 hours, however, the animal becomes more than usually responsive to stimuli, i. e., "nervous." Careful observation may reveal that his appetite and thirst increase. Furthermore, it may be demonstrated that, even when

he is at rest and undisturbed, his heart rate is abnormally rapid. Finally, it may be shown that his oxygen consumption (basal metabolism) has been augmented. If the dose of thyroxine is not repeated, these manifestations gradually disappear within the succeeding few days. If, however, such an animal receives a similar injection every other day, he rapidly loses weight, despite adequate amounts of food, and the tachycardia persists or increases.

It is a fact of considerable physiological importance that the effects of thyroxine persist in the hearts of such animals after isolation. Observations^{5, 8} have already been reported from this laboratory showing that the hearts and auricles of thyroxinized rabbits continue to beat, when completely isolated, at rates much faster than those of similar preparations from normal animals. The results of a large series of such experiments are graphically shown in Chart 3. This tachycardia characteristically persists for hours, tending to decrease with time far less

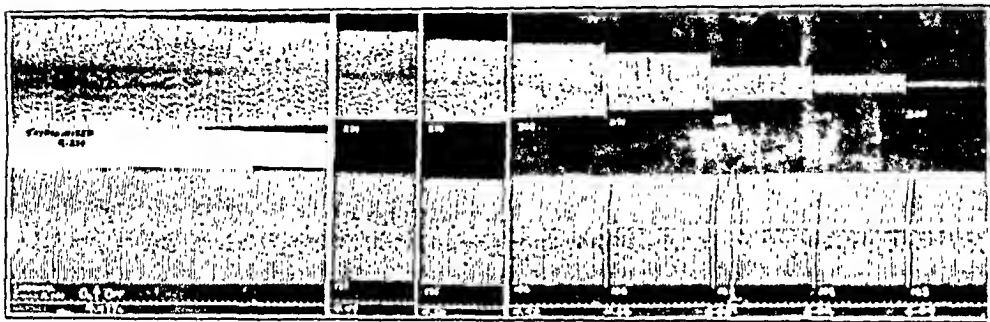


Fig. 1.—Effect of oxygen-want upon the auricles of normal and thyroxinized rabbits.

than the spontaneous rhythm of the isolated normal heart. This is in contrast with the tachycardia produced in animals by large doses of atropine or adrenalin, which subsides within a short time after isolation of the heart.

Further observations⁸ indicate that the isolated auricles of thyroxinized rabbits are more dependent upon the contemporary oxygen supply than are similar preparations from normal animals. The kymographic tracing recorded in a typical experiment is shown in Fig. 1. The upper record is that written by means of a light lever by the auricles of a thyroxinized rabbit; the lower that of "normal" auricles. Both were suspended in oxygenated Ringer-Loeke's solution in a Dale bath. In this experiment the auricles from the thyroxinized animal were beating at a rate of 234 per min., those of the normal at 140 per min. Interruption of the oxygen supply to the bath produced a conspicuously more pronounced effect upon the auricles from the animal which had received thyroxine.

By direct volumetric measurements it has been demonstrated⁷ that the isolated auricles from thyroxinized guinea pigs consume more oxygen per

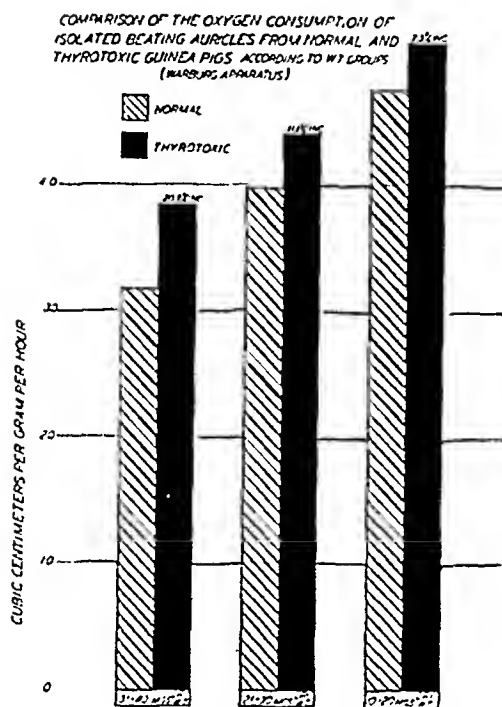


Chart 4.

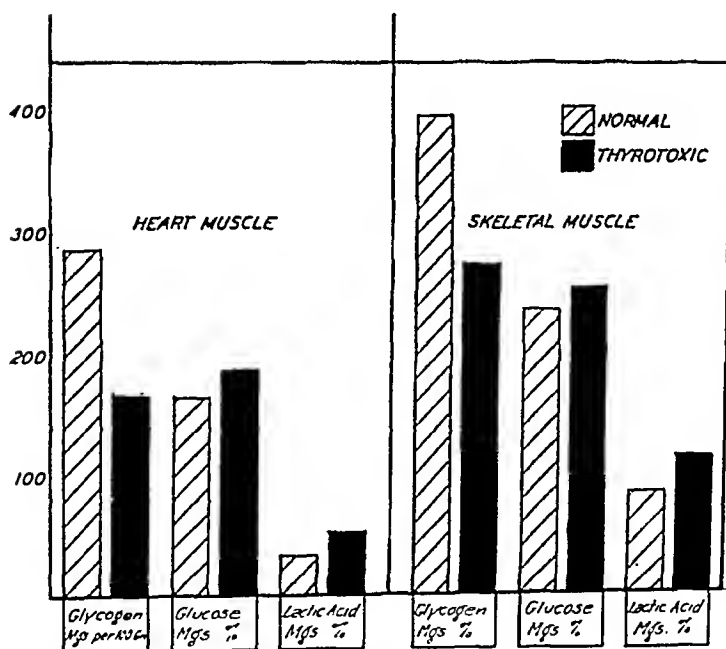


Chart 5.—Glycogen, glucose, and lactic acid content of cardiac and skeletal muscle from normal and thyroxinized animals.

gram per hour than those of the same weight removed from normal animals. These results of 31 experiments are summarized in Chart 4.

Dock and Lewis² have reported that the oxygen consumption per minute of heart-lung preparations from thyroid-fed rats is increased to the same extent as that of the entire animal. These authors state that such increase in the oxygen consumption of the heart-lung preparation can be accounted for by the increased weight and rate of beat of the heart of the thyroid-fed rat.

The discrepancy between the results summarized above and those of Dock and Lewis may be due, in part, to the difference in method. The guinea pig auricles in McEachern's experiments were surrounded and filled by fluid. Under these conditions the work performed is not significantly altered by change in rate of beat. In a number of instances the auricles ceased to beat during the period of observation. Under these circumstances no significant reduction in the rate of oxygen consumption occurred. This is in agreement with the observations of Clark and White,¹ who noted that the oxygen consumption of the auricles of cold-blooded animals was not significantly affected by rate of beat, provided no work was performed. In the heart-lung preparation, peripheral resistance and diastolic inflow remaining the same, a more rapid rate of beat is associated with an increase in the work performed.

That the metabolism of the myocardium is affected by the administration of thyroxine is further indicated by chemical estimations of certain constituents of the cardiac muscle of normal and thyroxinized rabbits. Chart 5 contrasts these results. The glycogen content of cardiac muscle is uniformly and conspicuously depleted by the action of thyroxine; the lactic acid content is increased in some instances. Similar alterations are demonstrable in the skeletal muscles of the same animals. That the glycogen content of skeletal muscle is depleted in thyroxinized animals has been previously noted.⁴

Such results do not in any fashion indicate that the heart is specifically or uniquely poisoned by thyroxine. They suggest rather that the metabolism of the myocardium is augmented thereby as is that of the skeletal muscle and other body tissues.

DISCUSSION

As has already been emphasized, the increased circulatory demands created by any conditions which augment metabolism increase conspicuously the work of the heart. In hyperthyroidism the metabolism of the myocardial tissue is also augmented. Conceivably these two factors combine in all cases, varying only in duration and degree, to bring to the fore the cardiac manifestations of the disease. The ultimate effect of these factors may be determined by the soil upon which they are implanted. In individuals whose circulatory reserve has been diminished by age or by organic cardiac disease they may result in myocardial in-

sufficiency. Presumably this may develop when the load thrown upon the myocardium exceeds or approaches the limits set by its own metabolism.

SUMMARY AND CONCLUSIONS

In a series of 200 cases of hyperthyroidism congestive heart failure occurred in 18.5 per cent. The average duration of symptoms was conspicuously greater in the cases with myocardial insufficiency. Its incidence increased in the age-decades above forty and was most common, in any age-group, in association with other, preexistent factors which tend to diminish the cardiac reserve: rheumatic heart disease, hypertension, arteriosclerosis or, more rarely, syphilitic heart disease.

Thyroxine 1/25,000 and desiodothyroxine 1/20,000 are without effect upon the isolated hearts or auricles of rabbits.

The administration of thyroxine to an animal (rabbit or guinea pig) so alters the metabolism of the myocardium that:

- a. The heart beats at an enhanced rate for hours after isolation.
- b. The oxygen consumption of the heart is increased, and
- c. The glycogen content of the cardiac muscle is diminished; in certain instances the lactic acid content is increased.

It is suggested that myocardial insufficiency may supervene in hyperthyroidism when the load thrown upon the heart exceeds or approaches the limits set by its own metabolism.

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(For discussion, see page 144.)

THE HEART IN HYPERTHYROIDISM—AN EXPERIMENTAL STUDY*

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THE constant association of varying degrees of cardiac irregularity, observed in different grades of hyperthyroidism, has led to many clinical observations and studies of the morbid anatomy in an endeavor to ascertain the rôle of the secretory product (thyroxin) in the production of such disturbances. The characteristics of the increased pulse rate, the modification of the electrocardiogram and the increased volume output of the heart have been studied by Sturgis and Tompkins,¹ Barker and Richardson,² Smith and Colvin,³ Hamilton,⁴ Willius,⁵ and Anderson.⁶ These authors have concluded that the heart rate is proportionate to the degree of thyrotoxicosis. That as a result of the increased rate and volume outflow, in the presence of increased metabolism, the heart at first dilates and then later hypertrophies. If the hyperthyroidism persists gallop rhythm, extrasystoles, fibrillation and final dilatation. The question has arisen as to whether such cardiac irregularities are attributable solely to thyroxin or to other factors such as age, the superimposition of thyrotoxicosis in the presence of arteriosclerosis of the coronary arteries or previously existing myocarditis. Hurxthal⁷ believes that there is a "specific heart drive" incited by thyrotoxicosis, while Lahey⁸ holds the opposite opinion pointing to the absence of specific pathological changes in the hearts in such instances and the relative infrequency of cardiac irregularities in younger individuals as compared with those in middle or advanced age. A difference of opinion also exists as to the presence of specific changes in human hearts associated with hyperthyroidism. Fahr and Kuhle⁹ and Goodpasture¹⁰ hold that fatty and parenchymatous degeneration, perivascular round-cell infiltration, fibrosis and granulation tissue formation occurring in the hearts of instances of hyperthyroidism are specific. Baust¹¹ and others oppose this view stating that there is no constancy in the findings and that it is not possible to exclude other factors.

Experimentally induced hyperthyroidism has been equally unsuccessful in solving the problem of the heart lesions in hyperthyroidism. Goodpasture,¹² Cameron,¹³ Hashimoto,¹⁴ Takane¹⁵ working with various animals (rabbits and white rats) were able to produce histocytes, round cells, perivascular necrosis and fibrosis in the heart muscle. On the other hand Lewis and McEachern¹⁶ and Rake and McEachern¹⁷ were not able to demonstrate specific lesions in the hearts of such experimental animals.

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Read by title.

It is therefore evident that neither the clinical nor the experimental data at hand are sufficient to settle the highly important question of the direct effect of the active principle of the thyroid gland upon the heart muscle in hyperthyroidism. Accordingly the following experiments were undertaken in an endeavor to further clarify this important and perplexing problem.

PROCEDURE

Twenty-four healthy Albino (white) rabbits were selected, weighed, housed in individual cages under careful sanitary conditions, and given standard prepared rabbit food (alfalfa especially prepared) once daily in sufficient amounts to maintain body weight under normal conditions. They were divided into four experimental groups as follows: Group I, Thyroxin fed and injected rabbits, Group II, Dessicated Thyroid (Armours) fed rabbits, Group III, Dessicated Thyroid (human thyroid glands from exophthalmic goiter) and Group IV controls. Six rabbits were placed in each group with the exception of the last in which there were five. In each of the Groups I, II, and III, two rabbits were thyroidectomized in order to remove the possible influence of the resident thyroid tissue. In addition one half of the animals (3 in each group) were given daily exercise by chasing them about in a large room for one hour. This was done to note the possible effect of additional strain upon the heart in the presence of hyperthyroidism.

The administration of the thyroid products was carried out by mixing them with the standard rabbit food and forming similar pellets which pellets were fed to the rabbits prior to the giving of the day's food portion. Great care was taken to see that each animal actually swallowed the daily dosage. The human thyroid tissue was obtained from 25 different thyrotoxic patients obtained through the courtesy of Dr. Thomas M. Joyce and Dr. Thomas D. Robertson of St. Vincent's Hospital and Dr. Charles Manlove of the Good Samaritan Hospital. These patients had an average metabolic rate of plus 27 and were given an average of 80 minims of Lugol's solution prior to the operation. The pathological diagnosis of all of these glands was diffuse parenchymatous hyperplasia (exophthalmic) with lugolization. The glands were cut into small pieces, dried and the fat removed with benzoin. The residue was dried, pulverized and intimately mixed. Titration revealed the presence of 0.019 per cent of iodine in the final preparation.

All control animals were kept and fed exactly as were those given the various thyroid products. An attempt was made to produce a continuous accelerated heart action by cutting the depressor nerves and denuding the carotid arteries of the carotid sinus investment, without success except in one instance, most of the animals dying within 48 hours, usually of some intercurrent pulmonary infection. One rabbit so treated lived for 6 days. The cause of death was not grossly manifest. All operative procedures including the final taking of the pulse rates and blood pressures by inserting cannulas into the carotid arteries was done with the intravenous administration of sodium barbitol (2.0 c.c. of 11 per cent per kilo of body weight) and in addition light ether anesthesia for the skin incisions.

The dosage of all thyroid products was administered orally and was based upon the body weight of the rabbit in comparison with the dosage of dessicated thyroid gland ordinarily given to human beings. The amount was stepped up sufficiently to insure toxic manifestations. Accordingly the rabbits in Group I were given 0.6 mg. of thyroxin by mouth for a period of eleven days following which they were given 1.0 mg. intravenously for twelve more days. The dosage was increased and given by vein because marked toxic manifestations failed to develop by the oral method, also because the supply of available thyroxin was becoming limited. The rabbits in Group II (Armours Dessicated Thyroid) were given 0.4 gm. daily for eleven days,

0.6 gm. for three days and 0.8 gm. for nine days. The rabbits of Group III (Human "exophthalmic" dessicated thyroid) were given the same dosage for the same time as those in Group II.

COMMENT

Not all of the rabbits reacted uniformly to the administration of the thyroid products (see Chart I). In general there was a progressive increased irritability, loss of weight and increased pulse rate. The irritability was most marked in Group III (Human Dessicated Thyroid) and least in Group I (Thyroxin), probably because of inadequate dosage in the latter group. The loss of weight ranged from 60.0 gm. to 1320.0 gm. It averaged 512.0 gm. in Group I, 531.0 gm. in Group II, 856.6 gm. in Group III and 130.0 gm. in Group IV (Control group). The greatest loss occurred in Group III. A number of these rabbits

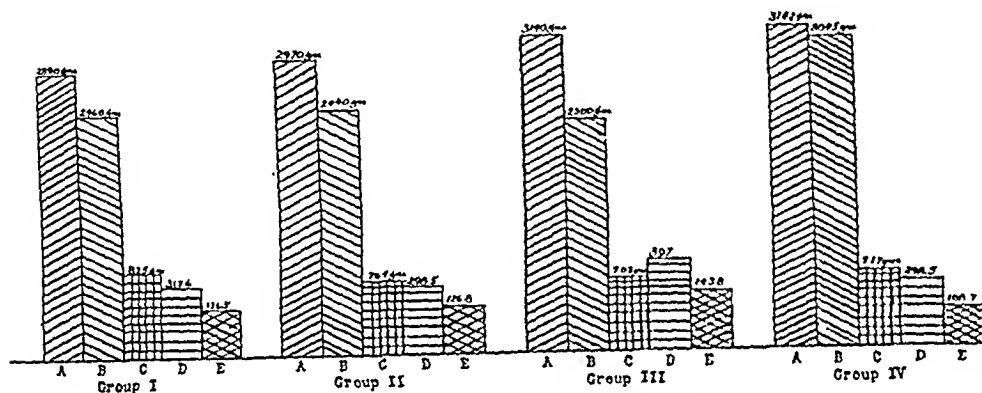


Chart Illustrating the Comparative Relationships Existing Between

- A- The average original weights
- B- The average final body weights
- C- The average weight of the hearts
- D- The average final heart rates
- E- The average final blood pressures

Chart I.—Illustrating the comparative relationships existing between A, the average original weights; B, the average final body weights; C, the average weight of the hearts; D, the average final heart rates, E, the average final blood pressures.

finally developed diarrhea with intense exhaustion. There was no doubt as to the evidence of a greatly increased metabolism accompanied by an increased respiratory rate and an accelerated heart action.

The pulse rate also increased progressively. It was taken daily throughout the experiment with the aid of the stethoscope. The rapidity of the heart action, which increased with the degree of thyrotoxicity, made it almost impossible to obtain an accurate count by this method. The beats appeared to be regular and full. There was no evidence of cyanosis of the mucous membranes of the mouth. The original pulse rate in Group I averaged 127.3, in Group II, 131.3, in Group III, 167.6 and in Group IV, 163. A consideration of the pulse rates taken with the stethoscope and finally with the recording drum indicates that the former method applied during the course of the experiment was inaccurate. While there was an increase of the heart rate in proportion to the degree of toxicity of the different experimental animals, there was no evidence of arrhythmia in the final recording. The pulse volume was

found to be smallest in those animals having the most marked increase in rate and the largest in those with slow rates. In the extremely thyrotoxic rabbits the heart exhibited signs of fatigue as indicated by the amplitude of the beats.

Considerable variation in the blood pressure was noted. It averaged 126.5 mm. Hg in Group I, 126.8 in Group II, 143.8 in Group III, and 106.2 in Group IV (The Control Group), the highest being 160 mm. Hg in a rabbit fed with dessicated human thyroid (exophthalmie), the lowest pressures being 115 in thyroid fed unoperated rabbits and 90 mm. Hg in thyroid fed thyroidectomized rabbits. In general the thyroid fed thyroidectomized rabbits had lower blood pressures; they averaged 117.6 mm. Hg as compared with an average of 142.3 mm. Hg in the thyroid fed non-thyroidectomized rabbits. This obvious increase in the blood pressures of thyrotoxic rabbits is in accord with the clinical findings in patients with hyperthyroidism, even when it occurs in younger patients in whom there is no reason to suspect other factors as a cause of the hypertension. One must therefore suspect that in hyperthyroidism clinically and experimentally the blood pressure is increased because of increased heart rate and possible angiospasm, probably due to either increased adrenalin output or excess metabolism (katabolism) or both.

All hearts with the exception of those from animals dying during the course of the experiments were weighed after being drained of their blood content. There was observed no constancy of relationship between the gross condition of the heart and the degree of toxicity of the animals. In general there was evidence of dilatation rather than hypertrophy. The chambers were large and the walls were proportionately thin. Although there were individual variations in the weights of the hearts in the different rabbits, the average weights in the 4 groups were found to be fairly constant (I—8.75 gm., II—7.64 gm., III—7.03 gm., IV—7.17 gm. respectively). The average heart weights of the first three groups when compared with the average original body weight established a ratio of 1 to 395.2 while the ratio between the average heart weights of the same groups and the average final body weights was found to be 1 to 314.8, a difference of 80.4 which in our estimation is largely due to the difference in body weights (original and final) rather than to a loss of weight in the hearts themselves. There was no gross evidence of disease in any of the hearts. In one or two instances the left ventricle appeared somewhat hypertrophic as compared with the right. Some of the hearts were long and narrow. The subepicardial fat was greatly diminished in the thyrotoxic rabbits as compared with those of the control animals. There was no detectable variation in the gross appearances of the hearts of the rabbits that were thyroidectomized or in those rabbits that were, in addition, exercised. There were no gross evidences of disease in any of the other organs or tissues of the rabbits as revealed by a general autopsy.

MICROSCOPIC STUDY

All sections of the tissues were stained with hematoxylin and eosin with additional van Giesen stains of the myocardium. The tissues and organs with the exception of the heart were studied mainly for the purpose of demonstrating the absence of other processes which might possibly explain the changes in the rabbits other than the induced hyperthyroidism. No disease processes were found. It was noted that the ovaries in the thyrotoxic rabbits apparently contained a greater number of so-called Call-Exner follicles than did the control animals.

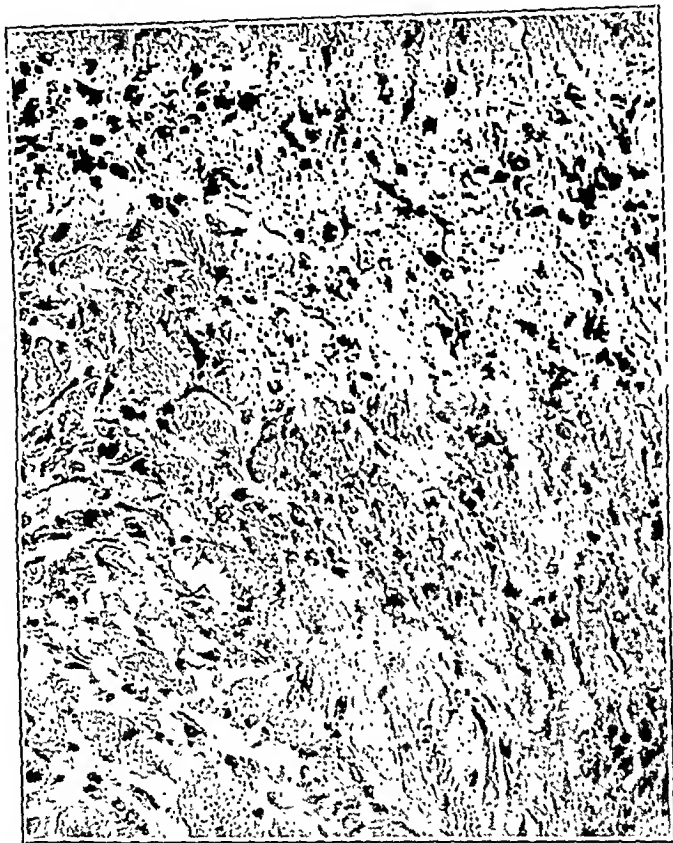


Fig. 1.—Photomicrograph No. 2. Rabbit No. 5. Illustrating the interstitial and perivascular diffusion of cells with the separation of muscle bundles.

For the study of the histology of the hearts sections were made through both ventricles at the apex, middle and base. In a number of instances of the hearts from the more pronouncedly thyrotoxic rabbits, every 300th section (10 mic.) was examined for the purpose of demonstrating the possible diffusion of disturbances. The histological changes in the hearts of the rabbits fed the different thyroid products varied considerably in the different animals. Such changes consisted of leucocyte invasion between the muscle bundles and about the blood vessels. These cells consisted of monocytes, plasma cells and eosinophiles. All but 4 of the 18 rabbits in Groups I, II and III exhibited such changes which were in some instances slight while in others such cell invasion was accom-

panied by some fibroblast proliferation with vacuole formation (fat) and fraying of the muscle bundles (see Figs. 1, 2, and 3). On the other hand only one of the rabbits in the control group exhibited such changes. This rabbit (No. 13) was one in which a tachycardia was produced by cutting the depressor nerves and destroying the carotid sinuses on both sides. This rabbit lived for six days. No gross pathological changes, except for a moderately enlarged heart, were found. Microscopically



Fig. 2.—Photomicrograph No. 2. Rabbit No. 9. Illustrating the cell invasion and fraying of muscle bundles.

marked cellular changes of the type described above (Thyrotoxic rabbit hearts) in the left ventricle were found. In none of the instances was fibrosis (scar tissue) *per se* found. There was no striking difference in the histological changes of the exercised rabbits as compared with those at rest. Neither was there any marked difference observed in the myocardium in those animals that were thyroidectomized prior to the induction of hyperthyroidism. The pathological changes were all confined to the left ventricle where they were diffusely scattered. They were not particularly pronounced in the papillary musculature.

DISCUSSION

There can be no doubt about the majority of the rabbits in the three groups having developed a state of hyperthyroidism within the range of individual susceptibility. The most striking evidence of the hyperthyroid state in the rabbits was the loss of weight, the increase of the pulse rate and the rise in the blood pressure. It seems fair to conclude that the whipping up of the metabolism leads directly or indirectly to an accelerated heart action which may eventually lead to cardiac exhaustion. The absence of pronounced cardiac hypertrophy in the rabbits and the more frequent occurrence of dilatation is in accord with the responses in the heart in human beings. It is estimated that it requires

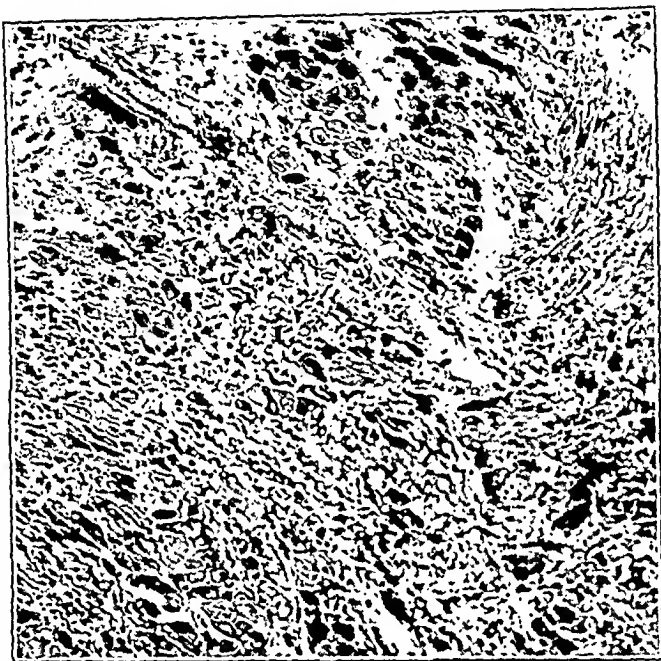


Fig. 3.—Photomicrograph No. 3. Rabbit No. 20. Illustrating extensive changes in myocardium.

approximately six weeks for hypertrophy of the heart to occur while these experiments extended over a period of twenty-three days. The striking absence of comparable pathological changes in the hearts of the control animals leads us to seriously consider cardiac damage in association with the induced hyperthyroid state in rabbits. As to whether this change in the heart is due to the actual impingement of thyroxin upon the cardiac circulation or musculature is difficult to determine. In arriving at a conclusion one must keep in mind the sequence of phenomena that evolve in the course of a slow or rapid perfusion of an excess thyroid secretion in the animal body. It seems to be a well established fact that metabolism (katabolism) is progressively and proportionately stimulated as a result of which the major body processes are augmented. Nutritional imbalance naturally follows. The glycogen reserve in the liver

(Willis and Mora¹⁷) as well as in the heart (De Fauw¹⁸) finally became exhausted. As this proceeds there occurs, according to Hsiao-Chien Chang and others,¹⁹ increased oxygen consumption and the increased transportation of metabolites, lead to the necessity of adjustment on the part of the circulation. There follows an increased pulse rate, augmented cardiac outflow, enlargement of the vascular bed and an increased blood volume. It is reasonable to conceive of the possibilities of the extra load placed upon the heart as eventually leading to fatigue and failure. It was in an endeavor to establish such factors that we provided the conditions of rest and exercise for our experimental animals, without success, probably because the conditions were not sufficiently sharply drawn. It occurred to us that the changes described might be related to the trauma of excessive, irregular and persistent overwork, on the part of the heart in the presence of hyperthyroidism, so that the myocardium might eventually undergo certain retrogressive changes (parenchymatous and fatty) on a nutritional basis. Further that such a degradation might lead to the tearing of muscle bundles and the secondary deposition of cells. Accordingly we attempted to provide a continuous acceleration and arrhythmia by cutting the depressor nerves and destroying the sinus carotici bilaterally. Only one of our rabbits survived the operation sufficiently long (six days) to permit of cardiac damage. In this the changes were extremely marked and of the same type seen in the rabbits rendered thyrotoxic by feeding. We intend to investigate further this phase of the problem.

It must be remembered in evaluating the results of such experiments as are here delineated, that experimental conditions may not be entirely comparable with the incipient disposition of clinically acquired hyperthyroidism which implies a dosage of thyroid secretion and a time element that cannot be duplicated experimentally. Clinical evidence cannot be expected to solve the problem. Certainly the majority of instances described and commented upon in the literature fall in the age group (forty and above) in which many different disease ravages may be expected to mask or modify any specific change attributable to thyroxin. For the same reason the study of the pathology of human hearts in such instances of hyperthyroidism cannot lead to definite conclusions. One cannot ignore the fact that clinically there is some relationship between certain irregularities of the heart and hyperthyroidism and that such irregularities are amenable to correction in younger individuals while in older ones they may be permanent and incurable by therapy and thyroidectomy. Experimentally there seems to be no question that damage may be produced in the hearts of experimental animals. As to whether such changes as we found in our experiments are due to the actual toxicity of thyroxin, *per se*, or to greatly altered circulation and metabolism phenomena will have to be determined by more extensive controlled investigations.

SUMMARY

Experimentally produced hyperthyroidism in rabbits using (1) thyroxin, (2) Armour's dessicated thyroid and (3) dessicated human thyroid (from patients having exophthalmic goiter) for a period of 23 days resulted in the following changes in the hearts: parenchymatous and fatty degeneration, histiocyte invasion, fraying of the muscle bundles and early fibrosis.

It is possible that similar changes might be produced by cardiac overwork irrespective of the presence of an excess of thyroxin in the circulating blood as is indicated by the results obtained by cutting of the depressor nerves and denuding the carotid sinuses of their investments in order to allow the heart to operate uncontrolled.

There is no evidence in the literature to disprove the fact that a heart, that is induced to work more rapidly, with an increased volume output in the presence of increased pressure and metabolism (as is true in hyperthyroidism) may not exhaust its nutrition and respond with morbid anatomical changes that may be erroneously ascribed to the pernicious impingement of thyroxin on the myocardium.

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CARDIAC STATUS AFTER PROLONGED THYROTOXICOSIS*

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THERE seems to be a growing tendency to question the existence of the "thyroid heart" (of Kraus). Recent pathological studies of McEachern and Rake,¹ Thomas,² Cabot,³ Lewis⁴ and others have cast great doubt upon the significance of findings reported by Goodpasture,⁵ Fahr and Kuhle,⁶ Goodall and Rogers⁷ and other workers which suggest that the hearts of patients dead of thyrotoxicosis show definite evidence of myocardial change. All of these pathological studies seem to be in agreement, however, that there is no change peculiar to thyrotoxicosis such as the characteristic lesions by which we identify rheumatic, luetic or arteriosclerotic heart disease.

Despite this lack of confirmation from the necropsy room, nevertheless, the impression seems to be generally prevalent that every thyrotoxic patient suffers a greater or lesser amount of myocardial damage. Thus the term "Hyperthyroid heart" is found in every classification of heart disease, and suggests that an intimate causal relationship exists between hyperthyroidism and the cardiac disorders which sometimes manifest themselves in thyrotoxic patients. Such a widespread clinical impression cannot be cast aside lightly. Where there is smoke there must be fire. Even though we suspect that the fire is a smudge fire and the excessive smoke therefrom is no sure measure of its size or heat we must investigate farther to discover the small flame of truth behind the widespread impression. Although demonstrable, organic evidence of cardiac damage is lacking yet it is possible that the heart is functionally impaired.

With the intention of ascertaining the amount and kind of functional impairment, I recently undertook a restudy of patients who were known to have been thyrotoxic for a prolonged period. This study was conducted in connection with a follow-up investigation of the late results of roentgen-ray therapy.⁸ To the cases of that series I have added several patients who had been thyroidectomized, all of whom were known definitely to have run a prolonged thyrotoxic course, and some of whom still have high metabolic rates after as long as ten years after operation.

An intensive study of this group seemed to promise information of a kind not usually found in studies of the thyroid heart. If injury to the cardiovascular apparatus is a frequent sequel of thyrotoxicosis we might expect this group to reveal it. Such a group, while it presents some disadvantages also possesses an advantage in that those patients given roentgen therapy may be considered to have run a longer course of thyrotoxicosis than if this course had been shortened by thyroidectomy. A

*From the Division of Medicine, Stanford University Medical School.

TABLE I

NAME	AGE	YEARS PT. WAS THYRO- TOXIC	HIGH- EST B.M.R. PER CENT PLUS	YEARS SINCE ONSET	B.M.R. AT LAST EXAM.	P.R.	B.P.	CARDIO- THO- RACIC INDEX	HEART AREA			MUR- MUR	EC- TOPIC BEATS	FAILURE		DIGI- TALIS	ELECTROCARDIOGRAM		
									PRE- DICTED	OB- SERVED	DIF- FER- ENCE			DYSP- NEA	EDEMA		P-T INTER- VAL	LEFT AXIS DEV.	T-WAVE IN- VERTED
Mrs. E. B.	44	1 1/2	23	11	-4	80	142/92	0.5	99	109	+10	0	0	+	0	0	0	+	III
Mrs. M. D.	54	5	112	10	-2	73	140/78	0.5	103	127	+24	0	0	0	0	0	0	0	III
Mrs. H. C.	50	1 1/2	67	10	-3	74	178/102	0.63	98	128	+30	0	0	+	0	0	Abn.	0	III
Mrs. E. C.	69	1	60	10	+2	68	160/100	0.5	98	119	+21	0	0	0	0	0	0	+	0
Mrs. E. B.	39	1 1/2	42	9	-1	71	124/86	0.44	89	92	+3	0	0	0	0	0	0	0	0
Mrs. R. M.	35	3	43	9	-1	72	134/90	0.45	109	98	-11	+	0	0	0	0	0	0	0
Mrs. B. S.	48	1 1/2	45	9	+4	78	120/76	0.6	102	107	+5	0	+	0	0	0	Abn.	+	III
Mrs. J. G.	55	4	46	11	+7	77	180/80	0.55	94	111	+17	0	0	0	0	0	0	+	III
Mr. K. S.	43	3	66	7	-6	60	116/80	0.49	106	132	+26	0	0	0	0	0	0	+	0
Mrs. H. S.	45	2	7	23	-8	78	172/94	0.41	89	93	+4	0	0	0	0	0	0	0	0
Mrs. A. F.	43	3	54	3	+10	80	142/94	0.46	95	80	-15	0	0	0	0	0	0	0	0
Mrs. G. B.	55	6	55	6	+27	104	150/76	0.44	98	100	+2	+	0	+	+	+	+	0	0
Mrs. F. S.	30	4	23	4	+24	98	118/78	0.47	89	112	+23	0	0	0	0	0	0	0	0
Mrs. M. G.	28	2	69	Oper. 12/31	?	90	136/70	0.43	82	84	+2	+	0	0	0	0	0	0	0
Miss E. A.	58	11	33	11	+30	112	134/64	0.55	85	81	-4	0	+	0	0	0	0	0	0
Miss M. M.	45	3	69	11	+20	76	146/96	0.51	101	102	+7	0	+	+	0	0	0	+	III
Mr. C. D.	48	6	61	7	-11	88	144/92	0.48	117	140	+23	0	0	0	0	0	0	0	0
Miss D. V.	15	1 1/2	40	Died Post- op.		86	120/50	0.5	94	106	+12	+	0	0	0	0	0	0	III
Mrs. E. M.	61	3	38	4	-16	90	175/95	0.45	113	93	-20	0	0	0	0	0	0	+	0
Mr. W. C.	51	1 1/2	33	2	-7	72	148/86	0.43	105	148	+43	0	0	0	0	0	0	0	0
MEAN	46	3	51	8 1/2		81	144/86	0.49			+9.8								

disadvantage exists, however, in estimating any cardiac damage caused by their former thyrotoxicosis because the time which has elapsed since they were thyrotoxic has seen many of them pass into the age of degenerative cardiovascular disease. This suggests that to estimate fairly the damage suffered by the heart in thyrotoxicosis we should confine our studies to patients under forty years of age. But when we recall that few, if any, thyroid-cardiacs are seen under forty we are led to suspect that the degenerative changes of the later decades are predisposing or complicating factors in the condition called "thyroid heart."

The data obtained from this follow-up study are shown in Table I where pertinent items obtained from an interval history and physical examination are supplemented by the objective findings of pulse rate, blood pressure, and heart size. An electrocardiogram was taken in every case and deviations from the normal are also recorded. Heart size was determined by a teleroentgenogram from which the cardio-thoracic index and cardiac area were measured.

The first ten patients may be considered as a group since all have normal metabolic rates from six to twenty-three years after treatment, and by every test may be regarded as entirely recovered from their thyroid disease. None of this group suffers from symptoms of cardiac disease. Two patients had dyspnea on exercise. One of these (E. B.) is twenty-five pounds overweight but her examination reveals no abnormal findings and she has a normal response to a simple functional test. The other patient (H. C.) has definite evidence of cardiovascular disease with blood pressure 178/102 mm. and enlarged heart, as well as electrocardiographic evidence of myocardial changes revealed in mild arborization block. This patient's age is fifty and she is known to come of a hypertensive family, which, with the very short course of thyrotoxicosis which she experienced, leads me to believe that her thyroid disease ten years ago played no part in producing her present hypertension. Her blood pressure at that time was normal.

Two others only in this group deserve comment. One (J. G.), fifty-five years of age, now has a systolic pressure of 180 and slight cardiac enlargement. One ectopic beat was noted at examination. This patient ran a long course, being under observation for over three years during which time she showed the characteristics, remissions and recrudescences of Graves' disease. In September, 1921, she was observed to have a pulse irregularity which the electrocardiograph revealed as a progressive auriculo-ventricular block in which every seventh or eighth impulse was blocked. This block and inversion of the T-wave in all leads suggest that her physician was giving her digitalis. Her electrocardiogram at the present time is normal. With her systolic hypertension we might suspect that thyrotoxicosis was an etiological factor in her case. This patient, however, was known to have had a blood pressure of 165 to 190 before she came under observation for thyrotoxicosis.

The other patient (M. D.), presented, in 1922, the most critical case of Graves' disease I have ever seen. Her initial basal metabolic rate was a little above one hundred per cent. After two months of hospitalization and roentgen-ray therapy, resulting in marked improvement, the metabolic rate was still plus eighty per cent. This patient's case history has already been reported in detail elsewhere¹⁹ and it suffices here to say that during the course of her thyrotoxicosis, which lasted over five years, she showed evidence of failing circulation in pitting edema of the feet and ankles. Now at the age of fifty-four this lady enjoys the best of health in every way, with no residuals of her former thyrotoxicosis and no signs or symptoms of circulatory disorder.

Included in this series are several patients who ran a very prolonged course, for reasons to be stated specifically for each case. Investigation of their circulatory systems for evidence of damage would seem to be a profitable procedure if the duration, rather than the intensity of thyrotoxicosis is the most potent factor in producing cardiac damage.¹⁰ Most of these patients can be dismissed without comment as they show no evidence of cardiac damage.

One patient (G. B.) was seen in consultation in 1925 when she presented a classical picture of Graves' disease. She was having auricular fibrillation at the time and was considered too ill for surgical intervention. She improved under medical care but has never been considered a good surgical risk and is now quite comfortable though her basal metabolic rate is plus 27 per cent and she has paroxysms of auricular fibrillation. She has dyspnea and slight edema of the feet, which had been noted four years previously. The daytime pulse rate is a little over one hundred per minute and her systolic blood pressure is 150 with a normal diastolic pressure. The heart's size is not increased. The electrocardiogram also shows no abnormalities and resembles one taken four years ago except that the earlier tracing showed frequent ectopic beats.

One other case (E. A.) deserves mention because of her very prolonged thyrotoxicosis and her relative absence of cardiac signs and symptoms, although she is now fifty-eight years of age. She has suffered from thyrotoxicosis for over ten years, had two lobectomies in 1922 and has subsequently run a course marked by remissions and recurrences with recorded basal rates as high as plus 33 per cent. She still presents signs and symptoms of toxic thyroid disease. She has no complaints referable to the heart and her blood pressure is 134/64 mm., with a suggestion of alternation noted when taking the systolic pressure. The heart size just exceeds the normal and the only electrocardiographic finding worth mentioning is slight widening of the QRS complex.

In summary it may be said that these patients who, from the duration and intensity of their thyroid disease might be expected to show the most characteristic and extreme cardiac damage, are singularly free from evidence thereof although they average forty-five years of age.

If one may draw the conclusion from this small group that there is scant evidence of serious, permanent cardiac damage in persons who have been thyrotoxic, there still remains the question: Whence comes all this cardiac smoke? Five years ago I¹¹ wrote that palpitation, tachycardia, arrhythmias, hypertension, and congestive failure, usually with auricular fibrillation, are the clinical findings which suggest cardiac damage in these patients, and pointed out that the first three cannot be accepted as certain evidence of cardiovascular disease. Neither is there anything about the hypertension, which is found only in older patients, that distinguishes it from ordinary hypertensive cardiovascular disease found alone or coincidental with other pathological states.

Auricular fibrillation which occasionally supervenes in the course of a thyrotoxicosis is a definite sign of functional abnormality. Its advent in this disease, however, does not presage its likely continuance or have the same significance that it does in rheumatic mitral stenosis. It scarcely ever occurs in patients under thirty, is often paroxysmal in nature and usually disappears with subsidence of the underlying thyrotoxicosis.

Congestive failure, usually with auricular fibrillation, occurs in a small per cent of thyrotoxic patients and constitutes definite evidence of myocardial insufficiency. This does not necessarily imply structural myocardial change, however, for congestive failure may supervene in a heart rendered temporarily functionally insufficient, but which is organically sound. This fact finds, perhaps, its best illustration in those cases occasionally encountered in which the manifestations of congestive failure overshadow the underlying hyperthyroidism. The existence of these cases has been pointed out by Levine¹² in his reports upon "masked hyperthyroidism," where long existing thyrotoxicosis has exhausted the cardiac reserve and led to congestive failure. As further evidence that it is functionally exhausted and not organically damaged I quote Levine who says of these cases that there is "no other type of heart disease from which a patient may so satisfactorily recover after reaching the extreme state of cardiac failure." Only recently we had such a case (W. C.) on the Stanford Service at the San Francisco Hospital. He did not cease fibrillating after thyroidectomy, as was expected, so quinidine was started on the nineteenth day after operation. His fibrillation stopped after the initial dose of five grains and he has remained regular without further quinidine medication.

From the foregoing it seems logical to conclude that the "thyroid heart" is in reality a heart which has exhausted its reserve through maintaining an augmented blood flow over a period of months, and sometimes years.¹¹ It is one prematurely aged by overwork rather than one damaged by a specific thyroid toxin. This viewpoint finds support in the investigations of Willis and Boothby who say that auricular fibrillation depends on the duration rather than the intensity of thyro-

toxicosis. In an extensive and carefully controlled study of heart size in thyrotoxicosis, Hurxthal and his co-workers¹³ found no definite relationship between cardiac enlargement and the duration of the thyroid disease. It is thus seen that there is no correlation between the severity of cardiac manifestations and the duration or intensity of hyperthyroidism. This brings me to the conclusion that inherent cardiovascular disease may be hastened in its development by the added work placed upon the heart in thyrotoxicosis; and that whether a toxic thyroid patient develops cardiac disease depends more upon the integrity of his cardiovascular system than upon the intensity or duration of his thyrotoxicosis. In addition I would emphasize that since the alleged thyroid-cardiac is nearly always past the age of forty years we should be cautious in assigning a previous, or coexisting thyroid disease as causative agent of the circulatory abnormalities which the patient presents.

SUMMARY

This is a clinical study aimed at ascertaining the amount of cardiac damage produced by hyperthyroidism. Since it is generally agreed that duration of the thyrotoxicosis, rather than its intensity, is the important factor in causing heart impairment, only cases of prolonged thyrotoxicosis are included here. The cases of twenty patients known to have been toxic for six months to eleven years were studied. Only one of these may be considered a cardiac cripple, and this patient had evidence of circulatory failure antedating the onset of thyrotoxicosis by four years. Two other patients (aged fifty and fifty-five years) had hypertension, which, from their histories could not be ascribed to their thyroid disease. There was no correlation between duration (or intensity) of thyrotoxicosis and heart size, blood pressure etc.

It was concluded that when cardiac failure supervened in the course of thyrotoxicosis it was a temporary functional insufficiency resulting from overwork (prolonged tachycardia, increased blood flow etc.), since there remained no evidence of permanent organic damage and because there is no characteristic pathological lesion. Further evidence in support of this view is that thyroid-cardiac disease is seldom, if ever, found in young people, but only in those in the later decades of life who have had their cardiac reserve already encroached upon by degenerative cardiovascular changes.

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MYXEDEMA HEART*

A REPORT BASED UPON A STUDY OF 17 CASES OF MYXEDEMA

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EIGHT years ago a woman aged forty-six years entered the Minneapolis General Hospital with the symptoms and signs of extremely severe heart failure; orthopnea, extreme anasarca, ascites, cyanosis, swollen liver (down 4 cm.), and passive congestion of the lungs. The heart was tremendously enlarged on teleroentgenographic examination, Ml. being 11.0 cm. and Mr. 8.0 cm. T. = 19.0 and total heart volume of 950 c.c. The electrocardiogram showed left preponderance, negative T₁ and iso-electric T₂. QRS duration = 0.18 sec. In addition the patient exhibited the symptoms and signs of a high grade myxedema: very slow speech, retarded cerebration, loss of memory, hoarse voice, dry and scaly skin, hair very sparse, dry and brittle, a sallow pallor of the skin with cyanotic patches over malar prominences, puffy eyelids with narrow lid slits, wrinkled forehead, all so typical of high grade myxedema. There was a very stubborn constipation. Basal rate even when associated with severe heart failure and dyspnea -25. Other data of interest; temperature 96-98, pulse rate 70. Blood pressure 110/70 mm. Red count 3,700,000, hemoglobin 75 per cent. Trace of albumin, few red cells and occasional hyaline and granular casts in urine.

The patient was given absolute rest in bed and put on fluid restriction and digitalis. No remission in the signs and symptoms of heart failure was observed on this treatment. Then large doses of thyroid extract (8 grams) were given and within a few days noticeable improvement in the symptoms of heart failure were noted. At the end of four weeks on thyroid extract, all dyspnea, lung edema and ascites had disappeared, the liver had receded to the costal margin; within twelve days the x-ray film showed the heart shadow 1.6 cm. smaller and in seven weeks' time the heart was normal in size, Ml. 8.6 Mr. 4.1 T. 12.7, heart volume 490 c.c. or one-half of its previous volume. The electrocardiogram became normal at the end of seven weeks. T₁ and T₂ were positive, the QRS time 0.08 secs. or 45 per cent as long as before thyroid treatment was instituted. The left preponderance had disappeared. The urine was free of albumin, casts and erythrocytes. The patient was now taken off thyroid medication and within seven weeks the heart had enlarged to Ml. 10.5 Mr. 5.5 T. 16, the T₁ and T₂ became negative, left preponderance appeared and the QRS became 0.16 sec. Moderate dyspnea and edema appeared and the liver came down below the costal margin. Thyroid was

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again administered and in six weeks the heart was normal in size, Ml. 8.5 Mr. 4.2 T. 12.7. The electrocardiogram showed T_1 and T_2 upright, the left preponderance no longer present, and the increased QRS time reduced to normal.

The patient remained practically free from heart failure symptoms for seven years. At times she would become careless about her treatment and then mild symptoms of myxedema would appear with lowered basal rate. At these periods heart failure symptoms would develop which would promptly disappear when thyroid extract in sufficient quantity was taken again. Two years after beginning treatment, the patient's blood pressure was 200/100 mm. and her basal metabolic rate 5 to 10 per cent above normal. On taking less thyroid the basal rate was brought down to -5 per cent but the blood pressure was up to 170/90. Moreover, the electrocardiogram showed a split and prolonged QRS of from 0.14-0.16 seconds. We feel that there is a very strong probability that this patient has a fairly high degree of coronary arteriosclerosis. In fact I believe it was present eight years ago when she first came under my observation. At that time I believe the coronary narrowing was very moderate. The split and prolonged QRS appeared then because of insufficient circulation in consequence of the drop in diastolic blood pressure as well as the drop in coronary flow associated with lowered minute volume. When the circulation improved on thyroid extract the diastolic blood pressure went up to 10-20 mm. Hg., the minute volume probably increased 50 per cent or more,¹ and the circulation through the coronaries was much improved so that the QRS time decreased in consequence of better blood flow to the heart muscle.* Later with increased narrowing of the coronaries a point was reached at which coronary flow was insufficient even with increased diastolic and systolic blood pressures. For the past four years the patient has been living in Oklahoma and writes me that she has some dyspnea and tires easily and notices a very moderate pitting edema of the extremities at bedtime. Although she has not been regular in taking her thyroid as she was previously, because of the difficulties of getting it immediately when her supply is exhausted, and probably is in need of better thyroid medication, yet I believe some of her cardiac symptoms are consequent upon coronary arteriosclerosis. I am hoping to have her come to Minneapolis for an examination in the near future.

No one can deny that the symptoms and signs of heart failure in this patient were largely consequent to the myxedema and were cured by thyroid medication after digitalis and rest in bed had failed. Her previous diagnosis made by very competent internists had been "myocarditis, chronic valvular disease, mitral insufficiency, myxedema." For

*Anrep² has shown that in the innervated heart-lung preparation if the diastolic pressure is kept constant, the coronary flow increases when the minute volume increases. The increase in coronary flow under these conditions is probably due to vasodilation reflexly produced.

me, the only real problem in this case is: how large a part did an associated coronary arteriosclerosis play? Certainly the amount of coronary disease present was in itself insufficient to produce heart failure. On the other hand it may very well have been an adjuvant factor and is now undoubtedly present along with a moderate degree of hypertension.

This case is a paradigm for five other cases of myxedema that I have seen in the past eight years, except that the electrocardiograms of the other cases showed normal QRS time. Eight cases of myxedema showed milder degrees of heart failure and less severe degrees of dilatation of the heart. But all of these eight cases showed some dyspnea, pitting edema, reduction of vital capacity, râles at the bases, dilatation of the heart on teleroentgenographic examination and very low iso-electric or negative T_1 , all of which disappeared on thyroid medication; in six cases without any rest in bed. Three cases of myxedema showed no signs or symptoms of heart failure. One case had mild heart failure symptoms and a moderately dilated heart. He would not remain under treatment long enough to find out whether the signs and symptoms of heart failure would recede under thyroid medication. Therefore we can sum up by saying that out of 17 cases of severe and moderately severe myxedema, 13 or 75 per cent showed symptoms and signs of heart failure, all of which disappeared after giving thyroid extract. The symptoms and signs were extremely severe in five (30 per cent) of our cases. I believe that these figures gathered from a study of seventeen cases give a fair representation of the status of myxedema heart or heart failure in hypothyroidism; namely 70-75 per cent will show some symptoms and 30 per cent will show a very severe degree of heart failure. Our oldest case was 70 years of age at the time symptoms and signs of myxedema and heart failure developed. Our youngest case developed symptoms and signs of heart failure and myxedema at 19 years of age. The arithmetical mean age for our 17 cases is 45 years for the approximate onset of myxedema heart.

There is to my mind no question as to what constitutes the proper therapy in most of these cases—thyroid extract sufficient to bring the basal rate to -5 to 0. When coronary disease seems definitely established, I would add a theophyllin derivative to dilate the coronaries. There is no objection to the use of enphyllin or other coronary dilators even when the diagnosis of coronary narrowing is not definitely established. I feel that digitalis is of little value in most of these cases. I have taken patients off thyroid, allowed them to become decompensated and then have tried the effect of digitalis in adequate dosage upon the case for periods of from two to three weeks, without a measurable effect. Thyroid would always show a definite effect upon these cases within an equal period of time.

Up to the present time no adequate explanation of myxedema heart has been given. Some years ago Sutherland Simpson of Cornell pro-

duced cretin sheep and goats by removal of the thyroid shortly after birth. Seventeen of these sheep and three of the thyroidectomized goats were given an autopsy examination by S. A. Goldberg,³ Professor of Pathology at Cornell Veterinary College. These animals had lived from approximately one to two years after the thyroidectomy. Causes of death were not stated, some were merely killed for autopsy purposes. At autopsy, the signs of ascites, anasarca, hydrothorax, hydropericardium, passive congestion of liver, passive congestion of lungs with lung edema, and passive congestion of the kidneys, one or more were found in 70 per cent of the animals. In a number of instances normal litter mates used as controls were autopsied at the same time. The controls never showed the above signs. All of the cretin animals showed arteriosclerosis and atherosclerosis of the large arteries with fusiform dilatation and lengthening, none of the controls did. The diagnosis of arteriosclerosis was made both macroscopically and microscopically. The majority of the animals showed anasarca, hydrothorax, and ascites. Only one showed a passive congested liver. But it is to be remembered that nothing is said about the livers in the other animals. The hearts of nearly all the animals are described as dilated, flabby, and pale. Goldberg also states that in the heart muscle of a number of these cretin animals, cross striation was absent, the muscle fibers were not normal in appearance. In this connection, it is to be remembered that Sutherland Simpson's daughter,⁴ Ethel, studying the voluntary muscles of the sheep, found that there was a distinct difference, namely that the cytoplasm of the muscles was very definitely in smaller quantity in the cretin sheep. The nuclei of the muscles in the cretin sheep were in much smaller number than in the normals.

If these autopsy examinations are to be accepted, then myxedema which was present in these cretin animals is frequently accompanied by signs of heart failure, of arteriosclerosis, and of changes in the heart and heart muscle which might be interpreted as due to or accompanying heart failure.

Kurt Felix⁵ has reported upon some experiments carried out under Friedrich Mueller in which it seemed to have been shown that thyroxin added to the perfusion fluid of an isolated frog's heart increased the amplitude of the beat or in other words, the work done per beat. Dynamometer and ergograph examinations of the voluntary muscles of myxedema patients from this clinic carried out by Professor Rockwell of the Department of Psychology of the University of Minnesota, show that the strength of the voluntary muscles is definitely reduced in myxedema and that myxedema muscles fatigue much more rapidly than the same muscles after thyroid treatment of the patient. It is not difficult to imagine that lack of thyroid hormone which leads to weakening and increased susceptibility to fatigue of skeletal muscle will lead to the same functional changes in heart muscle. There seems to be enough

experimental evidence then to make it seem very probable that lack of thyroid hormone weakens the heart and results in heart failure.

We are inclined to believe that not a few of these patients have some degree of coronary arteriosclerosis usually not of such a degree as to cause heart failure, but possibly aiding in the production of heart failure when myxedema develops and coronary flow falls because of the drop in diastolic pressure and because of the drop in minute volume. On the other hand the coronary arteriosclerosis is not to be assumed as the main

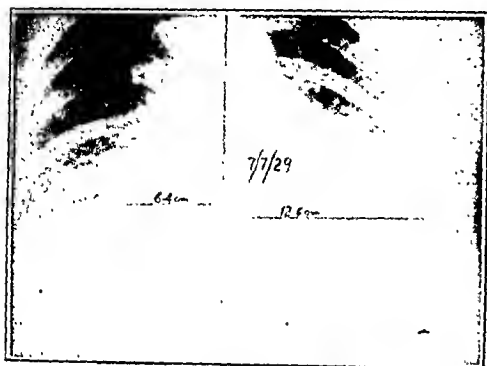


Fig. 1.

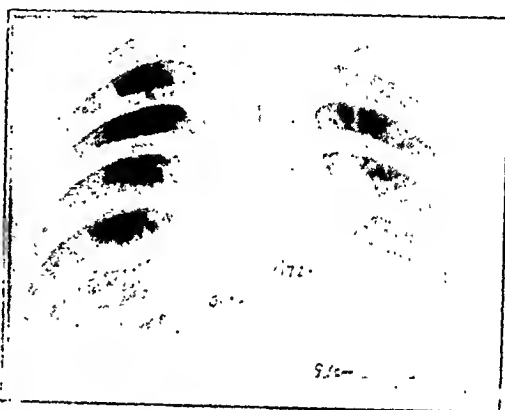


Fig. 2.



Fig. 3.

Fig. 1.*—Teleroentgenogram of a patient with myxedema on entrance; basal metabolism -27 per cent. Two weeks on large doses of digitals had no effect upon heart failure signs and symptoms.

Fig. 2.—Teleroentgenogram of same patient taken nine weeks later after being on thyroid extract for seven weeks; basal rate +15 per cent. Heart failure signs and symptoms gone.

Fig. 3.—Same heart after four months' withdrawal of thyroid extract; basal rate -32 per cent. Decompensation symptoms present.

factor in the production of heart failure in myxedema. One of our patients developed myxedema and heart failure at the age of 19 and in this case there is no reason whatsoever to assume coronary arteriosclerosis.

It is of considerable interest to know how long it takes to develop the severest grade of dilatation of the heart and heart failure symptoms after the function of the thyroid ceases. Zondek³ has reported upon a

*These illustrations are from a paper on Myxedema Heart by Jay Davis, Ann. Int. Med. 4: 733, 1931, and are reproduced with his permission.

case of a German officer who was shot through the thyroid gland in December 1914. Abscesses formed in the thyroid, destroying the gland. Approximately a year after the injury to the thyroid gland, symptoms of mild myxedema had developed and also a mild degree of dyspnea.

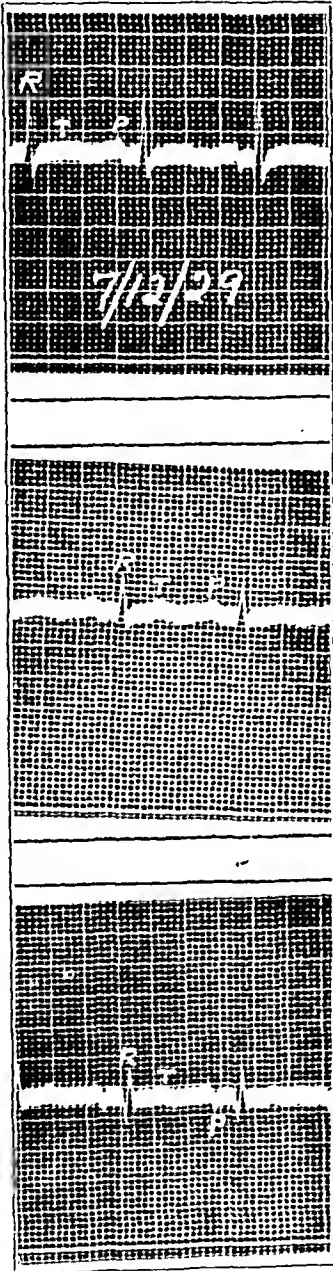


Fig. 4.

Fig. 4.—Electrocardiogram corresponding to Fig. 1.

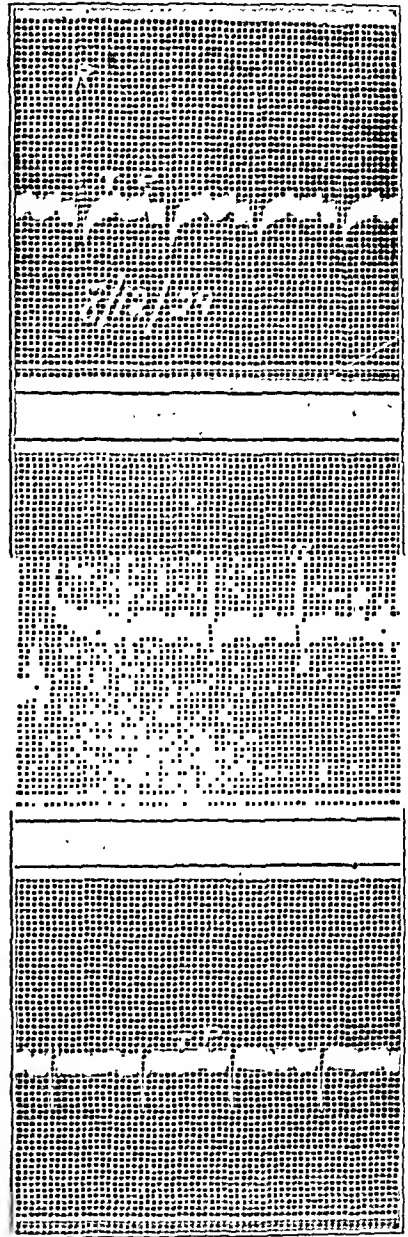


Fig. 5.

Fig. 5.—Electrocardiogram after thyroid treatment.

But it was three years after destruction of the thyroid gland before the severe stage of heart failure had finally developed.

The patient whose teleroentgenograms and electrocardiograms illustrate this paper was on thyroid extract for one year, at which time

there were no symptoms or signs of myxedema or of heart failure and the heart was normal in size, the transverse diameter being 12.9 and the basal rate + 3. The patient was then taken off thyroid extract and the basal rate immediately dropped, and within ten weeks' time was down to

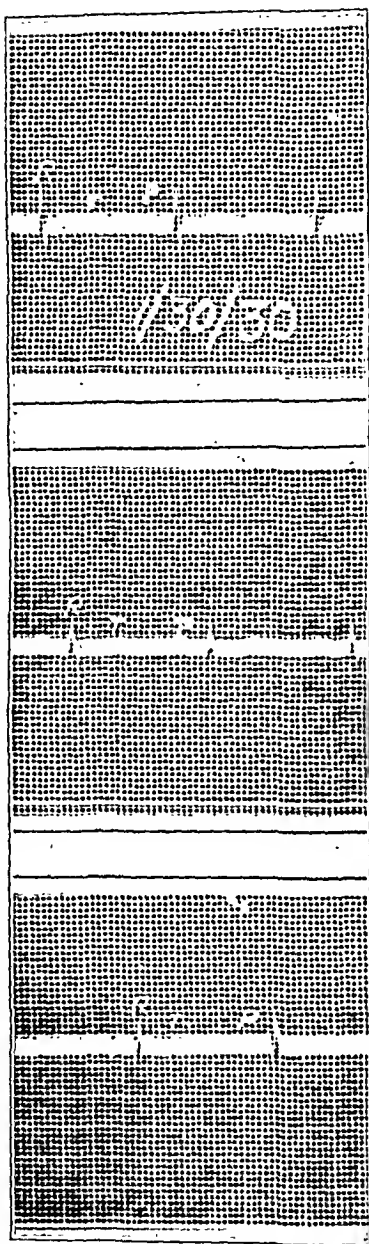


Fig. 6.—Electrocardiogram after withdrawal of thyroid extract.

-30. The patient was under constant observation in the wards of the hospital. No change of any kind was noted until about 12 weeks after thyroid treatment had been discontinued when the nurses reported that she was moving about more slowly and seemed to be less active. Very very slowly only did symptoms of myxedema develop. In fact, it was about

five months after discontinuing the thyroid treatment that the slowing up in cerebation and in physical activities became outspoken. Four months after discontinuing the thyroid extract, a little pitting edema along the shin bone could be made out and about this time the nurses and doctors noted that the skin was becoming dry. Two months after discontinuing thyroid extract, the heart was approximately the same in its size. Five months after discontinuing thyroid extract the heart had only dilated 1.6 cm. in transverse diameter. It was approximately eight months before the heart had dilated out about 3 cm. and dyspnea on exertion was fairly marked, the edema was moderately severe, and there were a few râles present in the bases of the lungs. Thyroid treatment was begun before the severest stage of heart failure was reached.

We feel certain that it would have taken a year or more before the heart would have attained its original transverse diameter and the symptoms of heart failure would have increased to their original severity. It is interesting to note that ten weeks after discontinuing the thyroid extract, the first signs of change in the electrocardiogram showed up. T_1 was then just barely positive. This experiment indicates that when the thyroid hormone is no longer supplied to a patient who has been supplied with sufficient thyroid hormone for a year or more, the mental symptoms of myxedema begin to develop within a few weeks. Skin changes appear a little bit later and are very slow in developing. But the changes in the heart, although they are indicated within a few months after discontinuing thyroid, yet it is many months before they develop to their extreme degree. Our patient living in the hospital had few calls upon her physical activities and it is barely possible that, if she had been at home and compelled to carry out more physical activity, the heart would have dilated more rapidly. Our studies seem to indicate that the severest grades of myxedema heart are only found in patients who have been in a hypothyroid state for a number of years. Where we are fairly certain that the hypothyroidism has developed within a period of less than a year or where the hypothyroidism is of mild degree, there we have noted that the dilatation of the heart and the symptoms of heart failure are of very moderate extent. Undoubtedly patients who for one reason or another are compelled to carry out considerable physical activity develop their symptoms more rapidly than those who can slow down their physical activities when the slowing down of mental activity takes place.

Christian⁶ has insisted that thyroid treatment may be dangerous in the treatment of myxedema associated with heart failure. I wish to report on a case of myxedema with heart failure complicated by a severe degree of coronary arteriosclerosis with improvement in the symptoms of congestive heart failure on thyroid treatment but ending in death from coronary thrombosis four months after beginning the thyroid medication. This case will not only serve to point out the danger associated

with thyroid treatment but will, I think, show why thyroid treatment is occasionally dangerous in these cases.

This patient, a female, forty-six years old, came to the University dispensary complaining of slow speech, slow activities, both mental and physical, loss of memory, mental depression, hoarseness, dry thick skin, loss of hair, cold hands and feet, all of about two years' duration, having gradually developed to the present degree. For the past two months she had noticed shortness of breath with swelling of ankles. She had several attacks of severe precordial pain the past four months. During these attacks she was very much frightened and was afraid she would die. These attacks sometimes came on without exertion, but more frequently after exertion and were then relieved on resting.

On examination the patient talked very slowly, skin was dry, hair was very thin, skin over face was sallow with cyanotic spots on the cheeks, face and eyes swollen, narrow lid slits, finely wrinkled forehead, nose broadened, lips and tongue swollen, no typical myxedema of skin seen or felt, but rather dry, wrinkled and with distinct loss of turgor. There was slight pitting edema of the legs, liver down below the costal margin one fingerbreadth, râles at both lung bases. Orthodiagram showed a generally dilated flabby heart; $MI. = 10.3$ $Mr. = 8.3$ $T. = 18.6$. Transverse thoracic diameter = 23.0 cm. The lungs showed the fluoroscopic signs of passive congestion. The electrocardiogram taken at this time has been lost but the notes of the physician who read the electrocardiogram state "Delayed intraventricular conduction, $QRS = 0.12$, left preponderance, low broad T_1 ." Basal metabolism at this time when some dyspnea was present -20. One taken six days later was -25. The blood pressure was 140/104. The patient was put on 1 grain of Armour and Company's thyroid extract twice a day. Six days later she entered the Minneapolis General Hospital. In the six days' interim the patient had taken only a small amount of the thyroid extract prescribed. She was extremely nervous and apprehensive and was extremely difficult to manage, in contradistinction to the average case of high grade myxedema. On the first hospital day she had anginal attacks which were only relieved by morphine. Throughout her stay in the hospital, the patient had frequent attacks of nausea and vomiting. Two grains of thyroid extract a day were administered. In addition 0.1 gram Euphyllin five times a day to dilate the coronaries. There were no more anginal attacks until on the eleventh day when she had another severe attack, unrelieved by amyl nitrite but relieved by morphine. From this time on until her death, attacks of angina were present nearly every day and sometimes there were two or three attacks in one twenty-four hour period. Some of these attacks lasted forty-five minutes and were only relieved by large doses of morphine. There were some days on which no attacks appeared but the patient was undoubtedly in a "status anginosus." The blood pressure which was 148/100 mm. on the day of admission dropped to 104/80 mm. on the fourth day in the hospital and from this time on the diastolic pressure varied between 60 and 80 mm. Hg. The vital capacity which was 1400 c.c. on admission went up to 2000 c.c. or 80 per cent of her calculated normal within three weeks. In the meantime her edema disappeared, the liver receded behind the rib margin and the heart went down to $MI. = 9.2$ $Mr. = 5.9$ $T. = 15.1$ within five weeks' time a recession of 3.6 cm. in transverse diameter. It never got any smaller than this so that part of the dilatation in this heart was not influenced by thyroid medication and therefore was probably due to another cause. The basal metabolism was normal within about six weeks after entrance to the hospital. The electrocardiogram which showed a depressed S-T interval in the first lead ending in a T_1 which only rose 0.5 mm. above the iso-electric line showed very little change after thyroid medication. We concluded from this that coronary arteriosclerosis was probably present in this case in addition to myxedema.

For a time the patient seemed compensated and the anginal attacks became infrequent. It appeared as if the patient might be improving. But about three months after admission the anginal attacks became very frequent, orthopnea set in, the heart was shown to be dilated on x-ray examination. Three weeks later the patient died suddenly. Autopsy was limited to the heart. This weighed 475 grams. There was almost complete occlusion of the left descending branch of the coronary artery with a thrombus farther down in the lumen. The other two branches were narrowed. There was a necrosis of the heart muscle in the left ventricle indicating a thrombosis which must have been present for a few days. There was also a large mural thrombus in the left ventricle. There was fibrosis of the rest of the myocardium. It is possible that a piece of the mural thrombus became free and caused a cerebral embolus with sudden death.

It is no longer a question in my own mind that this patient should not have been given thyroid medication. The number of attacks of angina pectoris increased after giving thyroid treatment and very probably because of the thyroid. Autopsy showed that the patient had a severe degree of coronary arteriosclerosis. That part of the coronary system which dilates considerably when minute volume increases could not dilate in this heart. Therefore there was no increased flow of blood through these coronary vessels when the minute volume put out by this heart increased 50-100 per cent or more and the mechanical work of the heart muscle increased correspondingly. Moreover the drop in diastolic blood pressure which took place after the patient was put to bed in the hospital was a factor tending to reduce blood flow through these narrowed coronaries. We must not forget that there is flow through the coronaries during systole as well as diastole in feebly beating hearts whereas in vigorously contracting hearts, flow takes place almost entirely in diastole. The myxedema heart is a feebly beating heart and if the coronary arteries are hardened and no longer able to dilate and if the diastolic blood pressure does not rise, the flow through the coronaries is better in it than in the same heart after treating with thyroid extract and producing a stronger contraction. The blood supply to the heart muscle in relation to the work performed was very probably much less after than before giving thyroid extract. Probably in consequence of this, the attacks of angina pectoris increased in number. Probably the reduced volume of flow through the coronaries aided in the formation of the thrombus. We are compelled to admit that thyroid medication might better have been omitted in the treatment of this patient. On the other hand, I believe that thyroid extract should be given to patients with myxedema and coronary disease provided no angina pectoris is produced and provided the heart shows signs of better function. Not infrequently angina pectoris attacks disappear after thyroid treatment is started in myxedema. In these cases we must assume the coronaries can still dilate when minute volume increases. Moreover in most cases the diastolic pressure rises after giving thyroid extract and in consequence the coronary flow increases proportionately to this increase in diastolic pressure. It is a matter for the judgment of the clinician to decide

when to give and when not to give thyroid extract. It is nearly always safe to try thyroid extract out and base the medication upon the phenomena produced by it.

SUMMARY AND CONCLUSIONS

Seventy-five per cent of all of our cases of myxedema show some signs and symptoms of heart failure. Thirty per cent of all our cases of myxedema show very severe symptoms and signs of heart failure. The volume of the heart in these severe cases is increased approximately 100 per cent.

Thyroid extract relieves the symptoms and signs of heart failure promptly. Digitalis is of doubtful value. Many cases of myxedema heart are complicated by coronary arteriosclerosis. If the coronary narrowing is extensive, thyroid extract treatment may be contraindicated because the coronary flow may decrease at the same time that the mechanical work of the heart increases. In these cases if angina pectoris develops after treatment with thyroid extract or increases in frequency and in intensity or if the heart failure symptoms do not decrease, then thyroid extract should not be given or should be given in reduced amount.

The age of onset of myxedema heart varied between nineteen and seventy years of age. The average age being forty-five at onset.

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(For discussion, see page 146.)

CONGESTIVE HEART FAILURE AND HYPERTROPHY IN HYPERTHYROIDISM: A CLINICAL AND PATHOLOGICAL STUDY OF 178 FATAL CASES*

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IN ANY study of cardiac hypertrophy the selection of a standard by which hypertrophy may be measured is of the greatest significance, as it is obvious that the integrity of one's conclusions depends almost entirely on such a standard. Cardiac hypertrophy in hyperthyroidism would practically cease to be a problem if a universally accepted standard for the weight of the normal heart were available. Bell and Hartzell,¹ in 1924, discredited practically all the standards published up to that time by showing that the increase in the average size of the heart after the fourth decade was due largely to the inclusion of cases of hypertension. Smith,³ in 1928, found that there was no relationship between age alone and weight of the heart, but that there was a definite correlation between the weight of the heart and the weight of the body if cases of hypertension and cardiac disease *per se* were excluded. At the same time he formulated a standard for cardiac weight based on bodily weight. In the present study we compared the weight of the heart at necropsy to Smith's maximal normal value for the usual weight of the patient prior to illness. It is probable that hearts weighing more than Smith's upper limit of normal values are hypertrophied.

It is almost self-evident that in the presence of hyperthyroidism the weight of the heart will depend on: (1) the weight of the heart before the onset of hyperthyroidism, and (2) any change in that weight which the hyperthyroidism might produce. Theoretically, at least, it is conceivable that hyperthyroidism might result in either an increase in cardiac weight as the result of increasing the work of each beat, or, under some circumstances, in a decrease as the result of malnutrition. There is little doubt that malnutrition in non-hyperthyroid states may result in cardiac atrophy. The hearts of patients dying of wasting diseases are usually small; victims of famine have been found to have small hearts, and in inanition, experimentally produced, cardiac atrophy can be demonstrated. A complete consideration of the effects of inanition on the heart may be found in the work of Jackson² on this subject. There is ample evidence in our material to indicate that loss of bodily weight in hyperthyroidism may be a factor in the determination of cardiac weight. Certainly the effect of malnutrition cannot be dismissed lightly when one considers that the average loss of bodily weight in our cases was about 25 per cent, and in some instances as high as 50 per cent.

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To present the problem more concretely the case is presented of a woman, aged sixty years, who came to The Mayo Clinic because of persistent exophthalmic goiter following thyroidectomy six years previously. Her usual weight was 135 pounds. At the time of death she weighed 67 pounds, a loss of 50 per cent. According to Smith's standard the weight of her heart before she was taken ill should have been between 203 and 286 gm. What was happening to the weight of her heart while her bodily weight was decreasing to 50 per cent of its former amount? If there were no other factors at work, her heart in all likelihood would lose a considerable portion of its weight. How much it would have lost we do not know. But during her illness her heart was confronted with the burden of mobilizing metabolites at a rate of 98 per cent more than normal. At death the heart weighed 300 gm., 14 gm. more than Smith's maximal value for a woman weighing 135 pounds. What conclusions are we justified in drawing from cases of this type? Can we conclude that the heart was spared while the body as a whole lost weight, or that the heart hypertrophied to the extent of 14 gm., or that the heart would have been much larger had not the loss of bodily weight tended to prevent hypertrophy? The present study was undertaken with the hope that we might be able to sharpen our conceptions of the problem, rather than to formulate any final opinions.

The material for study consisted of 110 fatal cases of exophthalmic goiter and sixty-eight fatal cases of hyperfunctioning adenomatous goiter, observed at The Mayo Clinic over a period of ten years ending January, 1931. In all instances the clinical diagnosis was verified by histological examination of the thyroid gland. Complete necropsy was performed in each case. In the entire group there were 129 females and forty-nine males, distributed through all the decades from the second to the eighth inclusive. Except for eleven patients aged more than sixty years, the cases of exophthalmic goiter can be divided into three groups approximately equal in number: patients aged less than forty years; patients aged between forty and fifty years, and patients aged between fifty and sixty years. Except for ten patients aged less than fifty years and two aged more than seventy, the patients with hyperfunctioning adenomatous goiter were distributed about equally in the sixth and seventh decades; twenty-five of the entire series were aged less than thirty-five years. The latter group was studied separately because of the relative infrequency of hypertension and degenerative lesions of the heart occurring in patients of this age. The relatively large number of fatal cases of exophthalmic goiter among young persons can be explained by the fact that although the series of cases extends over a period of ten years, compound solution of iodine in the treatment of exophthalmic goiter was in use as a routine only in the last eight years of the period.

Most of the patients had suffered from severe hyperthyroidism, as shown by the fact that only twenty-four of the patients with exoph-

thalmic goiter had determinations of basal metabolic rate lower than +50 per cent.

It is important to evaluate carefully the facts regarding the material which we have used for study, as, in a sense, it is selected. Since it is relatively unusual for hyperthyroidism to terminate fatally, a consideration of post-mortem observations alone may possibly lead to a distorted picture of the disease as it usually occurs. Furthermore, we are considering cases in which, as a group, severe long standing hyperthyroidism had been present, and our conclusions therefore may not apply to mild cases of short duration.

Of the 178 cases, eighty-eight (49 per cent) had to be excluded from the study of hypertrophy because of hypertension, recognized clinically or because of intrinsic disease of the heart recognized at post-mortem examination. One case was excluded because the weight of the heart was not recorded. All patients with a recorded diastolic blood pressure reading of 90 mm. of mercury or higher were considered to have hypertension. Most of the patients had several blood pressure readings recorded, and if at any one time a diastolic blood pressure reading of 90 mm. of mercury was obtained, we considered the patient to have hypertension and excluded his case from the study of hypertrophy. We do not maintain, however, that we have thereby eliminated all patients who may have had hypertension prior to the onset of hyperthyroidism. Furthermore, as hyperthyroidism sometimes causes a transient elevation of the diastolic blood pressure it is possible that some cases in which hypertension was not present have been excluded. An analysis of the remaining eighty-nine cases which consisted of sixty-nine cases of exophthalmic goiter and twenty cases of hyperfunctioning adenomatous goiter revealed the following:

1. In fifty-seven cases of exophthalmic goiter and sixteen cases of hyperfunctioning adenomatous goiter, a total of seventy-three cases (82 per cent), the hearts weighed less than 400 gm.

2. In eleven cases the heart weighed less than 250 gm.; in twenty cases it weighed between 250 and 300 gm., in forty-two cases between 300 and 400 gm., and in fifteen cases between 400 and 500 gm. In one case the heart weighed 530 gm.

3. When a comparison of the weight of the heart was made with Smith's standard maximal value for the usual weight of the patient prior to illness, it was found that in 49 per cent of the cases the actual weight of the heart exceeded the maximal standard value. It is highly probable that such hearts are actually hypertrophied. If the actual weight of the patient at the time of death was used as a basis for comparing the weight of the heart to the standard, it was found that in practically all instances the weight of the heart exceeded Smith's maximal values.

4. A study of the cases of seventeen patients aged less than thirty-

five years without hypertension or intrinsic disease of the heart showed that the heart weighed less than 400 gm. in sixteen (94 per cent) of the cases; in seven (41 per cent) of the cases the heart weighed between 300 and 400 gm., and in one case (6 per cent) it weighed more than 400 gm. Thirty-five per cent of the patients aged less than thirty-five years had cardiac weights exceeding Smith's maximal normal values.

5. There were only four patients whose cardiac weight was less than the normal minimal standard value. One of these patients was a girl aged fifteen years who had lost 48 per cent of her usual bodily weight. Another was a patient with mild hyperthyroidism of three months' duration, who died following a laparotomy done twenty-five days after thyroidectomy. The remaining two patients had lost respectively 37 and 44 per cent of their usual bodily weight.

6. In the eighty-nine cases under consideration there were sixty-six cases of exophthalmic goiter and twenty cases of hyperfunctioning adenomatous goiter.* These sixty-six cases of exophthalmic goiter could be separated into three groups: (1) thirty patients whose hearts might be considered to be hypertrophied, that is, the weight of the heart exceeded the maximal normal values by 20 gm. or more; (2) nineteen patients whose hearts might be considered as being normal or slightly hypertrophied, that is, the weight of the heart did not differ by more than 20 gm. from the maximal normal values, and (3) seventeen patients whose hearts weighed less than the maximal normal values by an amount exceeding 20 gm. A consideration of these three groups showed that the percentage of patients whose hearts exceeded the maximal normal values tended to increase in each succeeding decade, and that, conversely, the percentage of patients whose hearts weighed less than the standard tended to decrease in each succeeding decade. The percentage of patients whose hearts were approximately equal in weight to the standard varied independently of age. No constant correlation between the height of the basal metabolic rate and the weight of the heart could be found, although of nine patients whose basal metabolic rates were above +100 per cent, the weight of the heart exceeded the maximal standard in seven. It was also found that the majority of patients whose hearts weighed less than the standard or equaled it in weight had been ill for one year or less and that, conversely, the majority of patients whose hearts weighed more than the standard had been ill for much longer periods. These facts indicate that the duration of the hyperthyroidism is an important factor in the determination of the weight of the heart. A rough parallelism existed between the loss of bodily weight and the weight of the heart. Of the thirty patients whose cardiac weight exceeded the maximal normal standard, only three (10 per cent) had lost more than 30 per cent of the bodily weight, and of the seventeen

*Three cases of exophthalmic goiter could not be included because the usual weight of the patient prior to illness was not known.

patients whose cardiac weight was less than the maximal normal standard, eight (46 per cent) had lost more than 30 per cent of the bodily weight.

A consideration of the facts presented leads us to believe that in a given case of hyperthyroidism the weight of the heart at death will depend on the resultant of several factors, among which are: (1) the weight of the heart before the onset of hyperthyroidism; (2) the age of the patient; (3) the duration of hyperthyroidism; (4) the amount of excess work for each beat as the result of hyperthyroidism, and (5) the amount and rapidity of the loss of bodily weight. In a series of cases one would expect to find, depending on which factor predominated, cardiac weights ranging from subnormal values to values definitely indicative of hypertrophy.

CONGESTIVE HEART FAILURE

Congestive heart failure occurs as a manifestation of hyperthyroidism with such frequency that Moebius was led to believe: "Basedow patients suffer and die through their hearts." Since this dictum was formulated the pendulum has swung to the other extreme, so that now one frequently encounters statements to the effect that there is never failure of the heart in hyperthyroidism unless the heart has been diseased prior to the onset of hyperthyroidism. There probably is some truth in each of these attitudes, but there is reason to believe that neither is entirely correct.

Severe congestive heart failure manifested by edema of the lower extremities with ascites or hydrothorax occurred in twenty-seven cases (15 per cent) of the entire group of 178 cases under consideration. In nine of the cases of congestive failure no clinical or pathological evidence of hypertension or intrinsic cardiac disease was present, and it is probable that if the heart had been relieved of the burden of hyperthyroidism, health would have been restored to all of these patients, with the possible exception of one patient whose right auricle contained a ball thrombus.

In the remaining eighteen cases hypertension or intrinsic disease of the heart was present. However, in eight of these cases there was no clinical or pathological evidence to indicate that cardiac compensation and restoration of health would not have occurred if it had been possible to have controlled the hyperthyroidism. In the remaining ten cases the ultimate prognosis might have been questionable because of the presence of severe hypertension, nephritis or other cardiac disease even though thyroidectomy could have been performed successfully.

From the foregoing it is evident that of the twenty-seven cases of congestive heart failure restoration of health would probably have occurred in at least seventeen, if the hyperthyroidism could have been controlled.

It is unusual for congestive heart failure to appear during the course of hyperthyroidism in young patients. In this series of cases there were only two patients aged less than thirty-five years. One of them had hypertension and nephritis. The other, a man aged thirty-two years, had congestive heart failure, no cause for which other than hyperthyroidism was found. The weight of the heart at death of four patients with congestive failure was less than 300 gm., and of one patient it was only 205 gm. This patient was a woman aged forty-three years who had had exophthalmic goiter for seventeen months. She was admitted to hospital in a severe state of decompensation. On examination, edema of the legs, ascites and bilateral hydrothorax were revealed. The basal metabolic rate was +71 per cent. Auricular fibrillation was present. The blood pressure in millimeters of mercury was 162 systolic and 62 diastolic. An electrocardiographic tracing showed auricular fibrillation and an inversion of the T-waves in the derivations II and III. Under treatment the patient improved so that double ligation of the superior thyroid arteries could be performed, following which cardiac compensation was restored. She returned to the clinic three months later greatly improved. There was no evidence of the former decompensation except moderate edema of the legs. The cardiac rhythm was normal. Following thyroidectomy severe reaction occurred from which the patient died in less than twenty-four hours. At necropsy the right auricle and left ventricle were found to be markedly dilated, but the heart was otherwise normal. Undoubtedly there are many similar cases in which the patients do not die that are classified as cases of hyperthyroidism with independent disease of the heart because of the presence of congestive failure.

Auricular fibrillation occurred with increasing frequency in each decade in the 178 cases, and either auricular fibrillation or auricular flutter occurred in practically all of the cases of congestive heart failure. Clinically, one sees patients with hyperthyroidism who tolerate auricular fibrillation remarkably well. On the other hand, cardiac decompensation may occur in the course of hyperthyroidism when the auricles fibrillate so rapidly that a pulse deficit occurs; for example, the heart of the patient whose case history was just cited might not have been decompensated had the cardiac rhythm remained normal. In a study comprised only of fatal cases of hyperthyroidism it is impossible to evaluate auricular fibrillation as a factor in the production of congestive heart failure. In one of our cases congestive failure and death seemed to be the result primarily of a disturbance in cardiac rhythm. This patient was a woman, aged forty-three years, who had auricular flutter prior to thyroidectomy. After thyroidectomy normal rhythm was established. At the time of her dismissal from the clinic she appeared to be in good health. Apparently there was recurrence of the auricular flutter, for she returned to the clinic two months later with severe decompensation and

with an established auricular flutter. Death occurred shortly afterward. Post-mortem examination failed to disclose any intrinsic cardiac disease.

SUMMARY AND CONCLUSIONS

1. In eighty-nine fatal cases of hyperthyroidism, without evidence of hypertension or complicating disease of the heart, the weight of the heart in 49 per cent of the cases exceeded Smith's maximal standard values calculated on the basis of the patient's weight prior to illness.

2. The weight of the heart in a given case of hyperthyroidism depends on a number of factors, among which are: the weight of the heart prior to the onset of hyperthyroidism, the age of the patient, the duration of hyperthyroidism, malnutrition with its tendency to decrease the weight of the heart, and finally the amount of excess work placed on the heart as the result of hyperthyroidism.

3. In 178 fatal cases of hyperthyroidism severe congestive failure of the heart occurred in twenty-seven. Of these coronary sclerosis, hypertension, acute or chronic pericarditis, rheumatic endocarditis or syphilis were present in eighteen (67 per cent). In the remaining cases no cause for the congestive failure other than hyperthyroidism could be found.

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(For discussion, see page 149.)

STUDIES IN THYROID HEART DISEASE*

II. ANGINA PECTORIS AND HYPERTHYROIDISM

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IN A previous paper we¹ reported a series of cases of associated angina pectoris and hyperthyroidism. In that report we called attention to the fact that the association of angina pectoris and hyperthyroidism had been relatively little commented upon in the literature although known to occur. Since then, additional reports have appeared confirming the association of angina pectoris and hyperthyroidism. Levine² has noted the relief of anginal attacks after thyroidectomy. Haines and Kepler³ in a series of 33 patients with angina pectoris and hyperthyroidism report improvement of the anginal symptoms in the majority of their subjects after thyroidectomy.

It must be remembered that there are many causes for chest pain and that not all substernal or precordial distress means angina pectoris. One must exclude the pain and distress of mitral stenosis, aortic stenosis, pericarditis, endocarditis, aortitis, aortic insufficiency, etc. This we have endeavored to do in our present report.

There is no reason why a patient with angina pectoris may not develop some other disease, and conversely why angina pectoris may not occur in the course of another illness. On the mere basis of chance therefore, angina pectoris could be associated with almost any other disease. If, however, certain conditions occur more commonly than others in association with angina pectoris, and if, particularly, the removal and the eradication of these conditions is usually followed by relief and improvement of the anginal syndrome, then it is only logical to believe that the association was something more than merely casual or accidental. We believe it indicates a probable "cause and effect" relationship, and it is in this sense that we used the word "association" in the title of our first paper.

Angina pectoris has been associated with a number of diseases. It has been reported in association with the anemias,^{4, 5, 6} diabetes, tonsillitis and rheumatism, coronary disease and others. Syphilis, which was at one time believed to be a frequently associated factor in angina pectoris has been shown to be of very little significance. It is listed last in Kahn's⁷ report of over a dozen associated diseases in a series of 82 patients with angina pectoris. Nevertheless, it is our practice to make a Wassermann test and rule out syphilis in all cases of angina pectoris particularly when it occurs in younger individuals. Angina pec-

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toris has also been associated with excessive smoking⁸ and abdominal adhesions.⁹

In angina pectoris, male patients are in the majority while in hyperthyroidism, females have predominated. In the associated cases, females outnumber the males, five out of six in our previous series and seventeen out of thirty-three in Haines and Kepler's group. We are not certain why angina pectoris should be more prevalent in women with hyperthyroidism than in men. It may be a mere coincidence, or it may be that we see so many more women with hyperthyroidism than men, that complicating or associated conditions are therefore more likely to be also found in greater number among the female patients than among males.

FOLLOW-UP REPORT

In 1928 we reported six cases of associated angina pectoris and hyperthyroidism. Five of these had a subtotal thyroidectomy performed. Four of these were reported as having been relieved of their anginal pains for a period of from six to seventeen months at the time of our writing. The fifth patient was not improved and died a month after thyroidectomy. We have been able to follow up three of the surviving patients.

Mrs. I. H., aged fifty-nine years, had had typical attacks of angina pectoris for a number of years which had become especially more frequent, more severe, and more incapacitating in the two years prior to her admission to the hospital. A subtotal thyroidectomy was performed in January, 1929, for an exophthalmic goiter. She left the hospital nearly a month later after recovering from a postoperative bronchopneumonia. It is now over three years since her thyroidectomy. There have been no recurrences of any chest pain or distress to date. She is now able to walk in the cold and against a cold wind without any of the previous "severe grinding pain in the left chest and under the sternum" which often caused her to stop in her footsteps until the pain disappeared. The complete postoperative relief of anginal symptoms, which were becoming progressively more frequent and more severe, indicates, we believe, some relationship between the malfunctioning thyroid and the production of angina pectoris.

Mrs. A. B., aged fifty-nine years, suffered with angina pectoris for several years and an exophthalmic goiter which had become quite evident in the past year. These anginal pains were so pronounced that a surgeon in one of the hospitals dared do no more than a single polar ligation for the hyperthyroidism. This afforded no relief either for the chest pains or the hyperthyroidism, and the patient entered the Michael Reese Hospital several months later. On March 30, 1927, a subtotal thyroidectomy was done. For the next twelve months she was free of chest pains. In the latter part of 1928 and for a period of about six months she had mild infrequent substernal distress on effort. She then continued free of all anginal pains until November, 1931, when she had a sudden stroke (cerebral hemorrhage) while working in her kitchen at home and died 24 hours later without regaining consciousness. This case illustrates improvement of angina pectoris following thyroidectomy for an associated exophthalmic goiter. In addition, in this case, surgery was also followed by marked improvement of cardiac decompensation which was present for several years prior to thyroidectomy.

Mrs. A. J., aged sixty-two years, suffered with angina pectoris and an adenoma with hyperthyroidism for about seven months prior to her admission to Michael Reese Hospital, March 13, 1927. X-ray treatments to the thyroid failed to give relief. On March 29, 1927, after the usual preoperative preparation, a subtotal thyroidectomy was performed. We have seen this patient from time to time now over a period of 5 years. She is quite active for a woman of her years, and with the occasional exception of mild precordial discomfort following some pronounced nervous or emotional strain, she has had no recurrence of her severe anginal syndrome. This case illustrates improvement of angina pectoris following thyroidectomy for an adenoma with hyperthyroidism.

Report of new cases:

CASE 1.—Mrs. F. K. (A75342) housewife, aged forty-five years, had a thyroidectomy performed in June, 1926, for an adenoma with hyperthyroidism. She was not seen again until March, 1932. She stated then that following the thyroidectomy she felt well until two years ago. Since then she has been noting substernal pain coming after effort, on walking, particularly walking after a large meal or against a cold wind. The pain was also noticed following nervousness and excitement. The pain frequently radiated to left shoulder and arm and caused the patient to stop and rest until it disappeared. In addition, she had noted an enlargement in the region of the left lobe of the thyroid. Coincident with this she was becoming aware of increasing nervousness, weakness and insomnia.

Examination showed a pulse of 88 and a blood pressure of 210/100 mm. A firm, smooth nodule, the size of a hazelnut, was palpable in the left thyroid region. Two basal metabolism tests were 21.7 per cent above normal. Our impression was that this was a case of recurrent thyrotoxicosis with angina pectoris. The patient was put on Lugol's solution m. x t.i.d. p.e. She has now been under observation for one month. The chest pains have disappeared entirely. The relief of the anginal pains without any other restrictions or treatment is very suggestive. Surgical removal of the thyroid nodule is being considered.

CASE 2.—Mr. J. W., fifty-nine years old, tobacco merchant, seen in May, 1928 complained of pain in the chest for the past two years. This distress consisted of a severe pressing pain retrosternally coming on walking, stair climbing and after nervous excitation. The pain radiated at times to the right chest. Rest relieved the pain.

Examination showed: pulse 84; B.P. 190/110 mm.; Wassermann reaction, negative. Moderate exophthalmos; Von Graefe sign positive; thyroid negative to inspection and palpation. The heart was enlarged to the left and right and the second aortic tone was accentuated and booming. The liver dullness extended three fingers below the right costal arch but was not tender on pressure. Fluoroscopic and x-ray examination of the chest showed a non-pulsating mass the size of an orange in the superior mediastinum on the right side. The mass moved with deglutition. The trachea was moderately compressed and deviated to the left. Our impression was that this was a case of thyrotoxicosis (substernal thyroid) with angina pectoris.

A basal metabolism test made the next day was 7.6 per cent below normal. However, we continued to regard this as a case of hyperthyroidism. Following a series of x-ray treatments over the substernal mass in the next few months, his chest pains disappeared almost entirely and the substernal mass decreased in size. In November, 1931, his basal metabolism rate was 18.6 per cent above normal. He was then put on Lugol's solution m i to x B.I.D. in increasing doses. He has remained free of anginal symptoms up to the time of this report.

We believe this case is one of angina pectoris occurring in association with a sub-

sternal thyroid. Plummer¹⁰ and Morris¹¹ have reported cases of hyperthyroidism with normal or lowered basal metabolic rates with improvement after thyroidectomy.

CASE 3.—Mr. S. K., married, merchant, was diagnosed as a thyrotoxic case in December, 1925, at the age of fifty-seven years, and was given several x-ray treatments over the thyroid region. When seen again in August, 1929, he complained of substernal discomfort in the past eight weeks. One week ago he experienced a sudden severe pain in the region of the precordium accompanied by a sense of impending death. Pain was relieved by nitroglycerin under the tongue. Two basal metabolic rates were +51.1 per cent and +38.5 per cent respectively. Diagnosis at this time was angina pectoris and thyrotoxicosis. A month later he again complained of increasing precordial pains associated with effort and worry. A basal metabolic rate now was 55.9 per cent above normal. Ten days later after the usual preoperative care, a subtotal thyroidectomy was performed. Patient left the hospital a month later after recovering from a postoperative right lower lobar pneumonia. It is now over two years since the thyroidectomy. He has continued feeling well to date and has returned to active duties as executive of a large concern.

We have had other patients illustrating the same association of angina pectoris and hyperthyroidism, with relief of the angina pains following the administration of iodine and thyroidectomy, but for our present purpose, these three case reports will, we believe, suffice.

DISCUSSION

In angina pectoris associated with hyperthyroidism we would suggest that the already accelerated heart, working at a constant disadvantage, is more susceptible to any sudden or increased demands made upon it by exertion, nervous influences, etc. Such a heart, if it be competent, responds to these demands without the appearance of any distress; if not competent, pain may follow. The occurrence of angina pectoris in individuals close to or over fifty years of age, rather than in younger, hyperthyroid patients, suggests that in the former the heart may already be the seat of some vascular or myocardial changes and that the added burden upon such a heart by an increased body metabolism results in the heart being unable to meet still further some sudden demands upon it, and cardiac pain results. In young hyperthyroid individuals, with the myocardium and vascular supply intact, the hyperthyroid heart is still able to meet increased demands, and no pain results. We believe this to be the more likely explanation for the occurrence of angina pain in older thyroid patients.

We do not feel that angina pectoris in hyperthyroidism represents a separate entity due to any specific effects of the thyroid gland, but rather that in these hearts there is already some underlying groundwork for the occurrence of angina pains in the presence of hyperthyroidism.

The practical importance of this report is the recognition that angina pectoris and hyperthyroidism may and do occur in association with each other. The possibility of an offending thyroid should be more often considered and looked for in cases of angina pectoris. In elderly women

especially should the possibility of an underlying thyroid disorder be ruled out in cases of angina pectoris.

We are of the opinion that angina pectoris in cases of hyperthyroidism is no contraindication to thyroidectomy. We believe rather that surgery is strongly indicated. In our experience these patients, after the proper preoperative treatment, tolerate subtotal thyroidectomy about as well as other cases of hyperthyroidism in the hands of a competent surgeon. The postoperative relief of the hyperthyroid and angina symptoms in most of the patients justify, in our opinion, the surgical steps taken.

SUMMARY

Attention is called to the association of angina pectoris and hyperthyroidism. We believe that thyroidectomy is not contraindicated in the presence of angina pectoris, and have found that in the majority of cases relief of the anginal symptoms followed the use of iodine and thyroidectomy. The exact mechanism of the production of angina pectoris in hyperthyroidism and the interrelationship between the two conditions are not clearly understood at this time. We believe, however, that in such patients the underlying groundwork for the anginal syndrome already exists, such as coronary sclerosis with or without occlusion, myocardial fibrosis, aortitis, etc., and that the toxic thyroid (hyperthyroidism) is the additional burden which precipitates an anginal attack.

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(For discussion, see page 151.)

THE INFLUENCE OF THYROID EXTRACT AND HYPERTHYROIDISM ON THE ELECTROCARDIOGRAM, WITH SPECIAL REFERENCE TO THE T-WAVES*

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PROOF of a definite relationship between an increased metabolic rate and the form of the T-wave of the electrocardiogram would be invaluable in differentiating Graves' disease from other clinical conditions which are accompanied by tachycardia. Such definite proof is still lacking, though a certain type of T-wave of large amplitude and rolling contour has been noted in many cases of hyperthyroidism, and has been called a "thyroid T-wave."

Hoffman¹ in 1914 was the first to call attention to the high T of electrocardiograms in hyperthyroidism. He believed that the height of the T-wave paralleled the rapidity of the pulse.

In 1918, Krumbhaar² corroborated these observations, but in the same year White and Aub³ concluded that there is a very limited correlation between the rate of basal metabolism and the amplitude of the T-wave.

Pardee⁴ observed an increased height of the T-wave in definitely toxic cases of hyperthyroidism. Lewis⁵ stated that in thyrotoxicosis "except from the enhanced rate of beat and slight changes resulting therefrom, no definite alterations have been seen in the shape of the ventricular complex."

Willius⁶ has studied a large series of cases of hyperthyroidism electrocardiographically and noted that the T-waves are frequently unusually prominent, especially in lead 2.

Hamburger,⁷ in a series of cases, has reported the T-wave increased in height in several, but states that the increase is not uniform and has little, if any, relationship to the rate of the pulse.

Don and Langley⁸ in 36 cases of toxic goiter concluded that the size of T bears no constant relationship to the metabolic rate or clinical condition of the patient.

To determine any specificity of changes in T-waves during thyrotoxicosis the records in 222 cases were examined. After eliminating such extrinsic factors (which are apt to alter the T-wave) as digitalis, iodine therapy and complicating heart disease, there remained but 16 records. In 4 of these the rolling contour of the T-waves is beautifully exhibited. (See Figs. 1 and 2.)

The characteristic thyroid T-waves differ from the ordinary T-wave in their individual and peculiar contour. (See Fig. 3.) There is not necessarily an increase in their width or height although frequently

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they are of unusual duration and amplitude. As Lewis⁵ has stated that the changes of the T-wave in such patients are the consequence of an increase in the cardiac rate, electrocardiographic records of 25 cases exhibiting a sinus tachycardia from a variety of causes have been examined. None shows the high voltage or "rolling" T-waves which were seen in some of the cases of thyrotoxicosis. In addition, electrocardiographic records of 25 cases of neurocirculatory asthenia were studied, and much to our surprise T-waves quite similar to the so-called "thyroid T-waves"

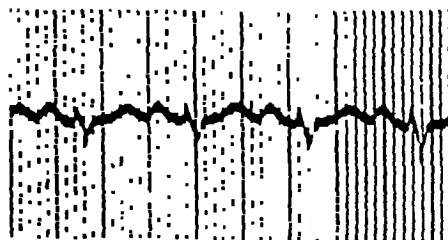
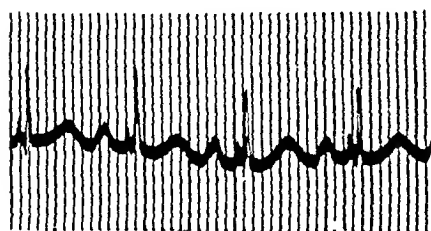
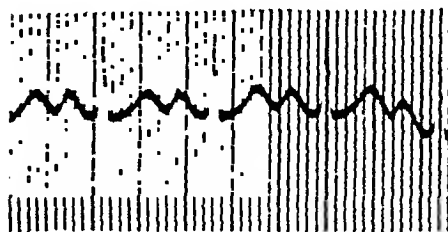
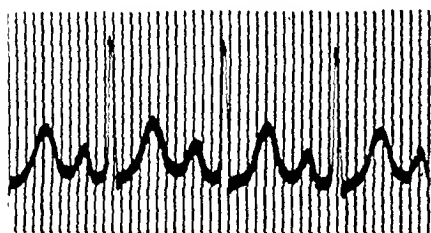
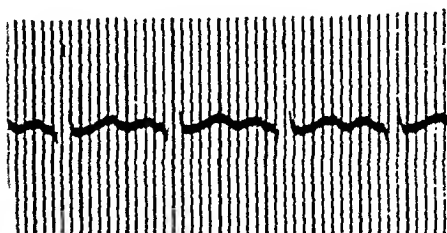
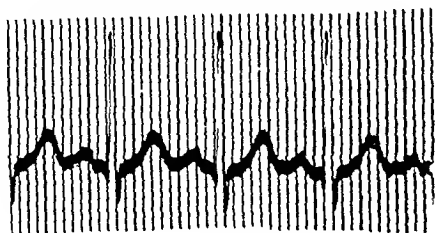


Fig. 1.

Fig. 2.

Figs. 1 and 2.—T-waves in hyperthyroidism illustrating the high voltage and rolling contour.

have been found in 5 and these in patients with a pulse rate of 90 or less. (Fig. 4.)

Because of the rather confusing results both in our clinical studies and in the literature pertaining to this subject, it occurred to us that the administration of thyroid extract to individuals without hyperthyroidism might be of interest. Five volunteers were selected and the records from 2 of the 5 cases are shown in Figs. 5, 6, 7 and 8. It should be mentioned that in Case 1 (Figs. 5 and 6), a patient with nephrosis, the basal metabolic rate was changed by medication from —30 per cent to

+25 per cent. This patient received 6 grains of thyroid extract daily for one month. In Case 2, a normal individual (Figs. 7 and 8), the control pulse rate was 80 and was increased to 130 by the administration

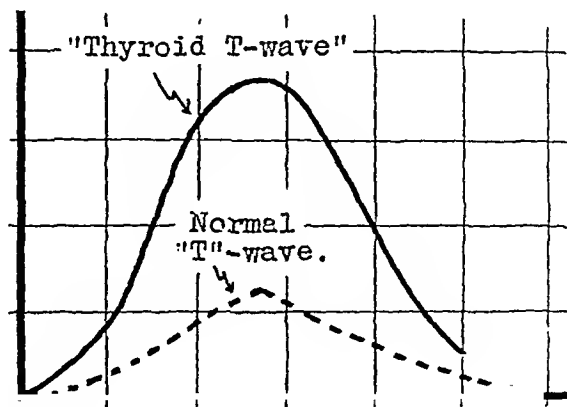


Fig. 3.—Diagram of "thyroid T-wave" (solid line) and normal T-wave (dotted line).

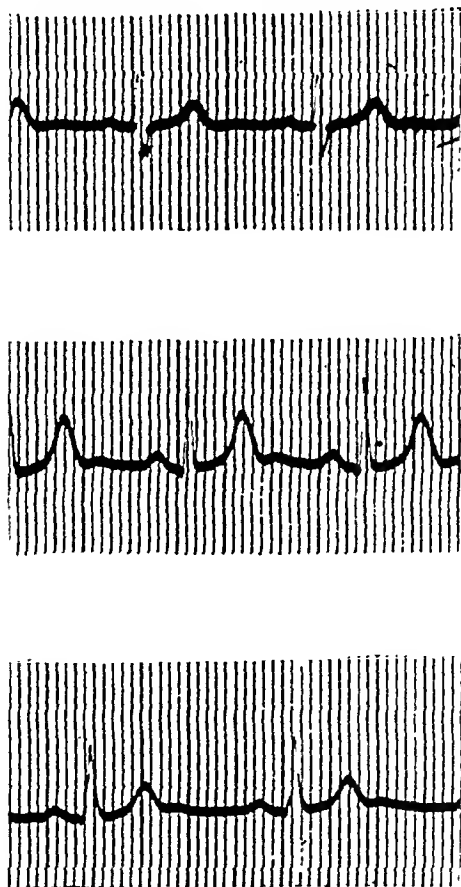


Fig. 4.—A T-wave in neurocirculatory asthenia simulating the thyroid T-wave.

of daily doses of 6 grains of thyroid extract for 2 weeks. In the remaining 3 cases there was an increase in the voltage of the T-waves but not to the same degree. Fig. 9 (the record of a patient with hyper-

thyroidism, a basal metabolic rate of $+33$ and pulse rate of 60) shows that the rate *per se* is not the specific factor which so remarkably influences the voltage and configuration of the T-waves.

As we were unwilling to administer toxic doses of thyroid extract to humans, it was decided to give large doses of this substance to normal dogs. In the first animal the cardiac rate in the control was 78 and the T-wave upright. Following the administration of thyroid extract, 20

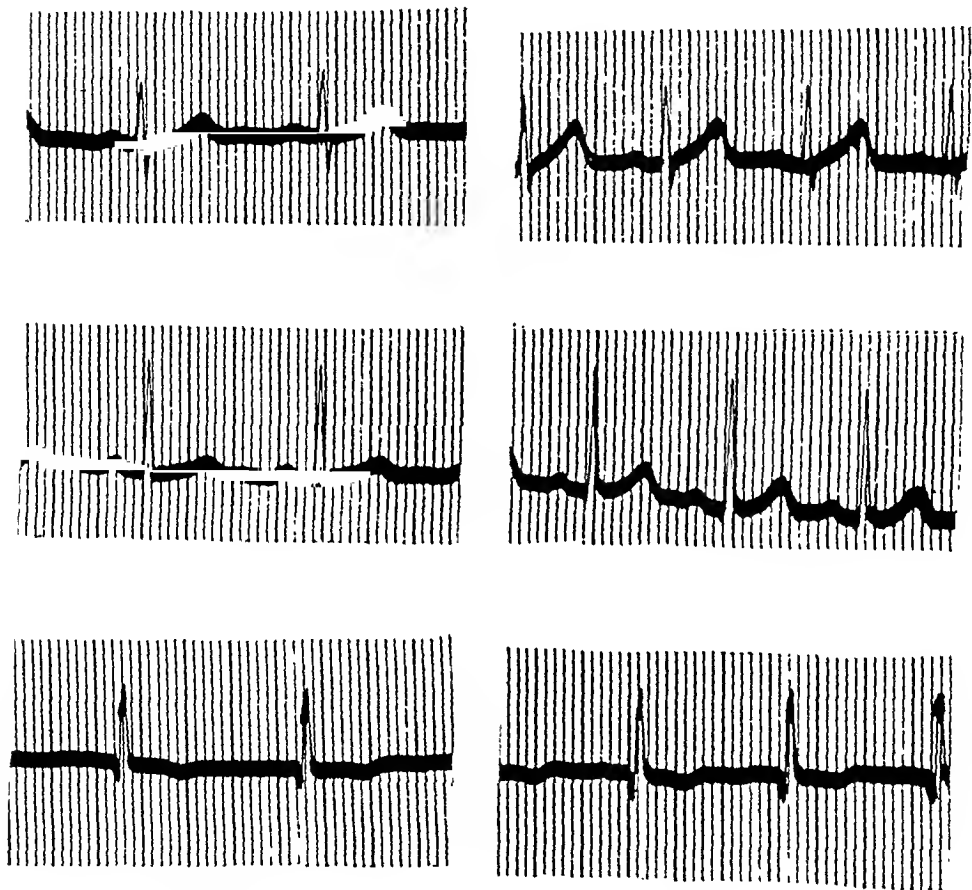


Fig. 5.

Fig. 6.

Figs. 5 and 6.—A case of nephrosis before and after thyroid medication.

grains daily for seventeen days, the rate increased to 120 and the T-waves became peaked.*

With a second animal both stellate ganglia were extirpated. Thyroid administration was then begun, 150 grains of thyroid extract being given in 33 days. One sees in the electrocardiograms that after operation the T-waves become negative and resemble in many ways those seen in cases of coronary occlusion, but this change is transient and in twenty-four

*We have been feeding 3 dogs with 20 grains of thyroid extract daily. In all the pulse rate attained a maximum in ten days and has subsequently been decreasing. The dogs are becoming increasingly irritable and are losing weight. The electrocardiographic and pathological findings will be reported later.

hours the electrocardiogram resembles the control record. During thyroid extract medication the T-waves again become negative and the rate progressively increases, reaching 120, after the dog had received 150 grains. At no time did the so-called thyroid T-waves appear in this dog or in any other dog in whom the T-waves were originally negative.

SUMMARY

It is apparent, therefore, that there has been no uniformity in the electrocardiographic findings in patients with thyrotoxicosis. The

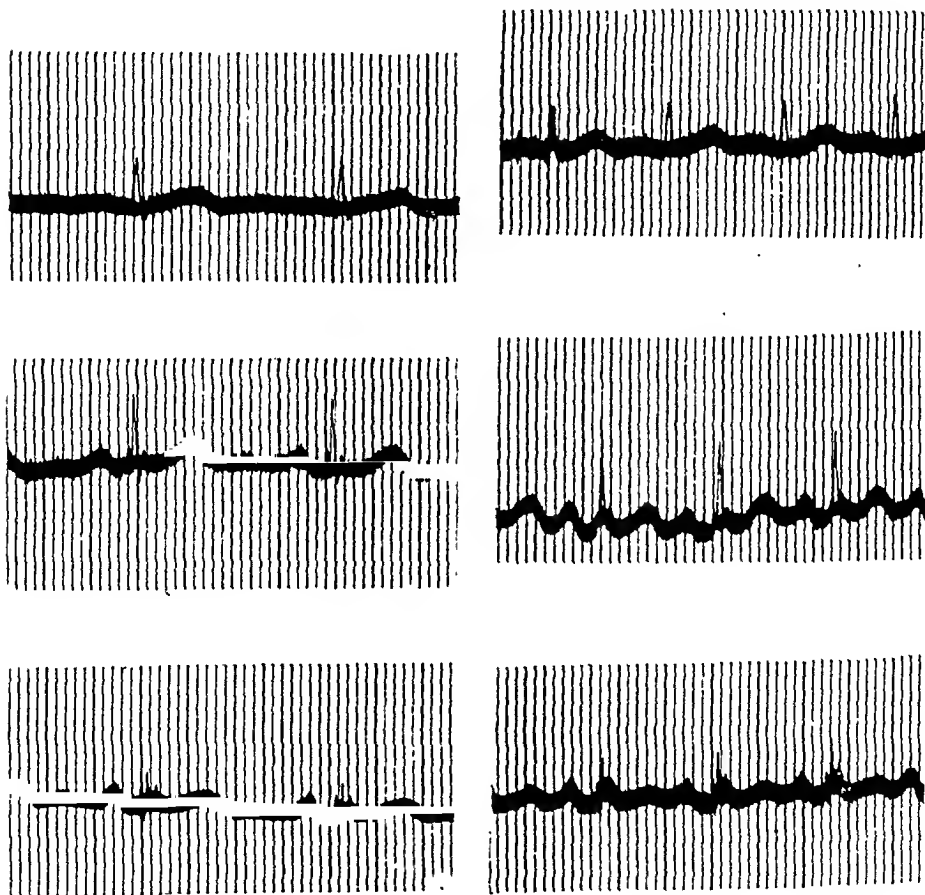


Fig. 7.

Fig. 8.

Figs. 7 and 8.—Electrocardiogram of a normal individual before and after administration of 84 grains of thyroid extract in seventeen days.

“thyroid” T-waves seem to bear no relation to the pulse rate nor to the basal metabolic rate. Furthermore, there is no constancy in their occurrence. Patients with marked degrees of tachycardia may fail to show T-waves of high amplitude and, conversely, with a slow pulse rate they may be encountered. This would seem to eliminate the heart rate as a factor in determining the height of the T-waves. And similarly it appears that the basal metabolic rate can be shown to have no relation to the amplitude of the T-waves. Characteristic, so-called “thyroid”

T-waves have been found in our records of patients with thyrotoxicosis with metabolic rates as low as -32 . Some other factor must be sought to explain their occurrence. This factor, we believe, is probably unrelated to the thyroid gland per se, since we have found similar T-waves in cases of neurocirculatory asthenia.

Since a high pulse pressure is common in thyrotoxicosis and is not infrequent in neurocirculatory asthenia, we are investigating its relation to the amplitude of the T-waves, but can express no opinion at the present time.

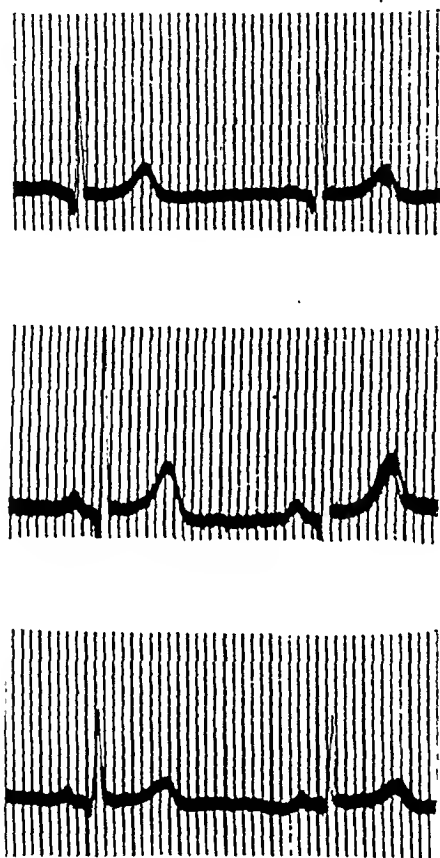


Fig. 9.—A case of hyperthyroidism, basal metabolic rate $+33$, pulse rate 60, illustrating a high voltage T-wave with low pulse rate.

CONCLUSIONS

1. The T-waves in the electrocardiogram of uncomplicated cases of thyrotoxicosis quite frequently are of unusually high voltage and of rolling contour.
2. These changes are not dependent upon the pulse rate or upon increased basal metabolic rate, and are not specific for thyrotoxicosis since they are seen also in neurocirculatory asthenia.
3. The administration of thyroid extract to normal individuals will produce comparable alterations in the human electrocardiogram.

4. In dogs the administration of large doses of thyroid extract causes tachycardia and increase in the voltage of the T-waves.

5. Removal of the stellate ganglia in one animal experiment did not prevent the development of tachycardia under thyroid medication.

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(For discussion, see page 151.)

AURICULAR FIBRILLATION IN GRAVES' DISEASE*

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ALTHOUGH the importance of the cardiac complications of Graves' disease† had long been recognized, auricular fibrillation, one of the most common and serious of these complications, received but meager notice prior to 1918. In that year Krumbhaar¹ called attention to its frequent occurrence in hyperthyroidism. Since 1923 many papers^{2, 3, 4, 5, 6, 7, 8, 9, 10} have appeared in which the various aspects of auricular fibrillation as a complication of Graves' disease have been discussed. The purpose of the present report is to present a brief summary of the study of 108 cases of auricular fibrillation in Graves' disease observed by us between 1923 and 1927.

In addition to these 108 patients observed personally by us, there were many other cases in which auricular fibrillation was observed or suspected by other members of the hospital staff. It is estimated that approximately 15 per cent of the patients with Graves' disease in this clinic during these years had auricular fibrillation. In general, it may be stated that only the more seriously and critically ill patients, or those in whom the cardiac manifestations of the hyperthyroidism were most prominent were referred to us.

A general survey of this series of cases reveals the following facts. Of the 108 cases studied, 74 had toxic adenomatous goiter, and 34 had exophthalmic goiter. The patients in the adenomatous group were somewhat older than those in the exophthalmic group, the average age of the former being 54 years and of the latter 47 years. The average age for the entire series was 51.5 years. The average duration of the thyroid enlargement was much longer in the adenomatous group, being 19 years as compared with 3 years for the exophthalmic group. The average duration of the so-called "toxic symptoms," however, was 1.4 years in the former and 1.5 years in the latter; and of auricular fibrillation 1 year and 0.8 year, respectively. Of the 74 patients with adenomatous goiter 56, or 76 per cent, were females, while only 14, or 41 per cent, of the 34 patients with exophthalmic goiter were women. The basal metabolic rate before treatment was somewhat higher in the exophthalmic group than in the adenomatous, the averages being plus 53 per cent for the former, plus 46 per cent for the latter, and plus 48 per cent for both groups combined. The mortality also was distinctly higher in the

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†The term "Graves' disease" as used in this paper is synonymous with the terms "hyperthyroidism" and "toxic goiter," and includes "exophthalmic goiter" and so-called "toxic adenomatous goiter."

exophthalmic group, being 38 per cent as compared with 22 per cent for the adenomatous group and 27 per cent for the entire series of cases.* In spite of these dissimilarities between the two groups, there were no significant differences from the cardiac standpoint, so that for the purposes of this study the entire series may be considered as a whole. This is in agreement with the conclusions of Kerr and Hensel.²

High grade congestive *cardiac failure* was much less common than might be expected, occurring in only 17 per cent of these cases. A slight grade of failure occurred in 46 per cent, while 37 per cent showed none of the usual signs of congestive failure, although shortness of breath and palpitation were common symptoms. Only half of the patients who died had cardiac failure and some of these had pneumonia, hemorrhage and other complications, which probably were important factors in the fatal outcome.

Auricular fibrillation in Graves' disease is much more often *transient* or *paroxysmal* than that due to other causes. In this series 25 cases, or 23 per cent, were of this type. Of these, 5 had auricular fibrillation only during a rather stormy postoperative period. The patients with paroxysmal auricular fibrillation did not differ materially from those with chronic auricular fibrillation with respect to age, duration of symptoms, or basal metabolic rate. Quinidine stopped individual attacks of fibrillation in some of these patients, and in many it either prevented the occurrence of attacks or reduced their frequency, while in others it appeared to have little or no effect. Of these 25 patients, 19 had thyroidectomy and 15 survived the postoperative period. These were all relieved of their fibrillation with the exception of one who had only hemithyroidectomy, and whose attacks were temporarily stopped but returned 3 months after operation.

The cardiac manifestations of Graves' disease may dominate the clinical picture and obscure the underlying thyroid disorder. Indeed, auricular fibrillation, apparently due to Graves' disease may appear before there is a significant elevation of the basal metabolic rate or any evidence that the work of the heart has been increased, as illustrated by the following cases.

One was the case of a woman 47 years of age, who had attacks of paroxysmal auricular fibrillation for three years. For a long time careful study revealed no evidence of Graves' disease or of any organic heart condition which might have caused the attacks. The heart rate and blood pressure were normal between the attacks. Finally tremor, loss of weight, diarrhea appeared; still the basal metabolic rate was only plus 13 per cent. Thyroidectomy was performed and the patient was completely relieved of these symptoms and of the attacks of auricular fibrillation for a period of at least 5 years.

The other case was that of a man, 21 years of age, who had attacks of auricular flutter in the spring of 1925 and again in October, 1925. Careful examination re-

*This mortality is high by present standards. The reasons for this, we believe, are that the most seriously and critically ill patients were referred to us, and that the full benefits of iodine were not obtained in the earlier cases.

vealed no abnormality of the heart or of the thyroid gland which might have caused the attacks. The blood pressure and the heart rate were normal during the normal rhythm. The basal metabolic rate was minus 15 per cent and minus 17 per cent upon two occasions in November, 1925. In March, 1927, there appeared nervousness, tremor, sweating, and flushing, and the blood pressure was 160/95 mm.; still the basal metabolic rate was only plus 1 per cent. In May, 1927, the patient developed very severe exophthalmic goiter from which he recovered entirely after subtotal thyroidectomy. There have been no further attacks of flutter.

In these two cases there is strong presumptive evidence that the cardiac disturbances were due to Graves' disease, but appeared before the Graves' syndrome was fully developed and before there was any evidence that the work of the heart was materially increased. Thyroidectomy after the Graves' disease was fully developed resulted in complete cure, with cessation of the attacks of abnormal rhythm. Three somewhat similar cases have been reported by Hamilton.⁹ Wishart¹¹ has also called attention to cases of this type. Other cases resembling these have recently been described by Morris,¹² Levine and Sturgis⁶ and Parkinson and Campbell¹³ have reported cases in which the cardiac manifestations were so prominent as to mask the underlying hyperthyroidism, even when the basal metabolic rate was elevated.

Digitalis is somewhat less effective in auricular fibrillation due to Graves' disease than in fibrillation due to other causes. On the average the amounts of the drug tolerated are larger, and the beneficial effects are less striking. Nearly all of our patients received a standardized tincture of digitalis, one cubic centimeter of which equalled one cat unit. It was given in doses of two cubic centimeters, three times daily, and was usually continued either until a satisfactory clinical response occurred or to the point of mild intoxication. The approximate tolerance could be estimated in 49 cases. If the average normal tolerance is 15 cat units per 100 pounds of body weight^{14, 15} and the average normal rate of disappearance of the drug is 1.4 cat units per day^{15, 16} (and this was in accord with the results obtained in patients with fibrillation not due to Graves' disease), then these 49 patients had a tolerance which was 134 per cent of the normal average. Four had a tolerance which was more than two and one-half times the average normal. Only one fell conspicuously below the average tolerance; she was a very obese woman of 63 years, with a basal metabolic rate of only plus 14 per cent, who developed nausea and ventricular rate of 64 after taking only 36 per cent of the theoretical digitalizing dose. Digitalization, carried out as described above, reduced the average ventricular rate in this group of patients from 119 to 90 per minute. The average basal metabolic rate of these patients was plus 48 per cent, the same as for the entire series of 108 cases. The response of some of these patients to the intravenous administration of ouabain or digifoline was determined and found to be on the whole less striking than that of patients with auricular fibrillation

not due to Graves' disease. In general it may be said that the patients with the higher basal metabolic rates have higher initial ventricular rates, tolerate larger amounts of digitalis, and show less ventricular slowing in response to digitalis. Exceptions to this rule, however, are common.

The most striking failures of digitalis to slow the ventricles were observed in the very toxic state which sometimes occurred shortly after thyroidectomy. While this state persisted large doses of digitalis given intravenously often failed to influence the heart perceptibly, and ventricular slowing occurred only after the extreme thyroid intoxication had passed off.

Some patients showed entirely satisfactory slowing of the heart by digitalis, and a few had slow ventricular rates before the administration of the drug. Most, but not all, of these were patients with relatively little elevation of the basal metabolic rate. Our experience in respect to digitalis is similar to that of Foster,¹⁰ Sturgis,¹⁷ and Grant,¹⁸ and is contrary to that of Kerr and Hensel² and Hamilton.⁹

Following successful treatment of the underlying Graves' disease, recovery from auricular fibrillation with the return of normal rhythm is usually prompt and striking. Restitution of the heart to normal is often complete in every respect. Our experience suggests that, generally speaking, the most satisfactory treatment for the cardiac manifestations of Graves' disease is partial or subtotal thyroidectomy. Only 53 of the 68 patients operated upon survived. This is a mortality of 22 per cent, and, when compared with the almost negligible postoperative mortality in Graves' disease without auricular fibrillation, emphasizes the well-known fact that the presence of auricular fibrillation is accompanied by a material increase in the risk of thyroidectomy.^{10, 19} Nevertheless the mortality was considerably higher in those who had other forms of treatment; 14 of the 40 patients, or 35 per cent, who did not have thyroidectomy, died. Some of these, of course, did not have thyroidectomy because it was thought they were in too serious a condition to withstand this operation. Furthermore, the degree of improvement is strongly in favor of surgical treatment, many of the patients who recovered from operation being restored to practically complete health while none of those who did not have thyroidectomy are known to have recovered completely.

Of the 53 patients who survived thyroidectomy 28, or 53 per cent, were completely relieved of fibrillation by operation alone. In only 7 of these did fibrillation persist for more than 2 weeks following operation. Of the other 21 patients, 13 had paroxysmal fibrillation which did not return after convalescence from operation. Two of the 28 patients failed to respond to quinidine after operation.

Of the remaining 25 patients, 14 were given quinidine which restored normal rhythm in 11, while the 3 in which quinidine failed, and the

11 others, who did not receive quinidine, continued to have auricular fibrillation and are not known to have returned to normal rhythm. All but one of the patients who failed to respond to quinidine developed toxic symptoms upon very small doses, so that the drug could not be given in adequate amounts. Most of the patients in this series who were given quinidine received the drug during the second or third postoperative week.

Six patients received quinidine preoperatively. In 3 of these normal rhythm was restored, but fibrillation returned in all during or following operation. Similar discouraging experiences with quinidine preoperatively have been reported by Sturgis,¹⁷ Hamilton,⁹ and others, while Foster¹⁰ and Read²⁰ advocate the administration of quinidine before thyroidectomy when fibrillation is present.

Of the 40 patients who did not have thyroidectomy, 6 received quinidine, with restoration of normal rhythm in 4. Of the 34 who did not receive quinidine only 1 stopped fibrillating; in the others the auricular fibrillation persisted.

Our experience suggests that thyroidectomy is at present the best treatment for Graves' disease complicated by auricular fibrillation. We believe that in addition to the usual preparation for operation these patients should be fully digitalized. Soon after operation, within a few days or a few weeks, quinidine may be given to those who do not return to normal rhythm spontaneously. In this manner one may expect to restore normal rhythm in approximately 90 per cent of the patients recovering from operation. When the normal rhythm follows operation spontaneously or in response to quinidine therapy it is usually permanent, no doubt because the cause of the fibrillation has been removed. The mortality, although considerable, will be less than in other forms of treatment and the proportion of patients restored to practically normal health will be very high. There is no other type of chronic heart disease in which so nearly a complete recovery is possible. The frequent spontaneous return of normal rhythm after thyroidectomy has been emphasized by Krumbhaar,¹ Hamilton,²¹ Sturgis,¹⁷ Dunhill, Fraser, and Stott,⁵ and Lahey.²² The value of quinidine in those cases in which fibrillation persists after thyroidectomy has been stressed by Dunhill, Fraser, and Stott,⁵ Lahey,²² Hay,²³ Anderson,²⁴ and others.

Cardiac hypertrophy is seldom pronounced in Graves' disease. Cardiac enlargement when present is due chiefly to dilatation. In some of our patients the clinical signs of considerable cardiac enlargement were confirmed by roentgenological examination. In others, however, the great overactivity of the heart gave the impression of considerable enlargement when the x-ray films showed little or no increase in the heart's size. In many, however, there were no signs of enlargement clinically or by x-ray. Of the 29 patients who died, 13 came to autopsy. The average heart weight in these cases was 438 grams. In only two instances did

the heart weigh more than 500 grams; in each of these it weighed 530 grams, and one of these two patients had hypertension during life.

In some respects the cardiac disturbances of Graves' disease resemble those induced by the toxemia of an acute infection such as diphtheria or pneumonia, especially in respect to the frequency of transient or paroxysmal disturbances of the cardiac rhythm, and the almost complete return to normal after recovery from the underlying condition. The rarity of pronounced cardiac hypertrophy suggests the operation of other factors than overwork of the heart. Those cases in which the cardiac disturbances, presumably due to Graves' disease, occur before there is any evidence that the work of the heart has been increased lend further support to this view. In fully developed Graves' disease, however, the work of the heart is obviously increased to a significant extent and this is undoubtedly one of the important causes of the cardiac complications of this disease.^{17, 20, 25} Difficult as it is to estimate the relative importance of the mechanical and the toxic factors, these observations suggest that the toxic factor is of considerable importance. Although this conclusion is contrary to the opinions of Hamilton,⁹ Lahey²² and others, it is in agreement with the views of Goodpasture²⁷ and Plummer.²⁸

SUMMARY AND CONCLUSIONS

A study of 108 cases of auricular fibrillation in Graves' disease, observed between 1923 and 1927, is presented. The incidence of this complication in this clinic during those years was approximately 15 per cent.

The average age of the patients studied was 51.5 years. The average basal metabolic rate was plus 48 per cent before treatment; mild or severe cardiac failure was present in 63 per cent; and the mortality for the series was 27 per cent.

Auricular fibrillation due to Graves' disease is more likely to be transient or paroxysmal than that due to other causes. In this series 25 cases, or 23 per cent, were of this type.

The cardiac manifestations of Graves' disease may dominate the picture and obscure the underlying thyroid disorder; they may even antedate all other recognizable signs of the Graves' disease causing them. Two cases are cited in illustration of the latter observation.

Digitalis is less effective than in fibrillation not due to Graves' disease. The amounts tolerated are on the average larger and the beneficial effects are less pronounced. The digitalis tolerance could be estimated in 49 instances. In these the average tolerance was 134 per cent of the theoretical normal tolerance, and the effect of digitalization was to reduce the average ventricular rate from 119 to 90 per minute. In the very toxic states which sometimes followed operation large doses of digitalis intravenously did not influence the ventricular rate materially.

Following successful treatment of the underlying Graves' disease, recovery from fibrillation is often prompt and striking. Restitution of

the heart rhythm to normal is often complete. Thyroidectomy followed by the use of quinidine in those patients in which normal rhythm does not return spontaneously soon after operation may be expected to restore normal rhythm in approximately 90 per cent of the cases.

Cardiac hypertrophy is seldom pronounced. Enlargement, when present, is due chiefly to dilatation. The average weight of the hearts of 13 patients coming to autopsy was 438 grams. The two heaviest hearts weighed 530 grams each.

In some respects the cardiac disturbances of Graves' disease resemble those induced by the toxemia of an acute infection. Although it is difficult to estimate the relative importance of the increased work the heart must perform as compared to the toxic factor, the infrequency of hypertrophy and the character of the cardiac disturbances suggest that the latter is of great importance.

The writers desire to express their gratitude to Dr. F. A. Collier and to others of the Department of Surgery for the opportunity of observing some of the patients included in this study.

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(For discussion, see page 152.)

THE INCIDENCE OF AURICULAR FIBRILLATION AND RESULTS OF QUINIDINE THERAPY

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THIS report is based on a study of the patients from the surgical services of Dr. Crile and Dr. Dinsmore during my association at the Cleveland Clinic from 1923 to 1931. It includes 426 patients with auricular fibrillation who had a complete thyroidectomy, which permitted the study of final results. During the same period there were approximately 150 additional patients with hyperthyroidism and auricular fibrillation who, for one reason or another, never had a complete thyroidectomy and hence are not included in this report.

The incidence of auricular fibrillation in patients with hyperthyroidism has varied in different years from 6 per cent to 9 per cent, but during the year 1930 it was 8.3 per cent and in 1931 it was 8.9 per cent. I think these figures represent an accurate proportion. In 1928 only 5.87 per cent of patients with hyperthyroidism presented this heart complication. This was a year when there was an unusually large number of patients with hyperthyroidism and also an unusually large number with symptoms which had persisted for only short periods, in some for only one to three months, and in such a group, I think, one might expect a smaller incidence of auricular fibrillation.

The beginning of this period (1923) antedates the routine preoperative use of iodine as advocated by Plummer, and at that time ligation of thyroid arteries was being done in 60 per cent of the patients at the Cleveland Clinic. Following the institution of the routine use of iodine, it was found that ligation of the arteries was almost never necessary, and now it is done only occasionally. Lobectomy or thyroidectomy is usually done at the first operation; this has reduced the mortality considerably.

In a series of 2400 cases of hyperthyroidism, 18.5 per cent were in men and 81.5 per cent were in women. Of patients with auricular fibrillation and hyperthyroidism the ratio was 30 per cent males to 70 per cent females. This would seem to corroborate Means and Richardson's impression that men are inclined to have a more severe form of hyperthyroidism than women.

The oldest patient in this entire series was aged seventy-two and the youngest was eighteen years of age. The average age of the men was forty-nine years, and of the women fifty-one years. The average age for all patients with auricular fibrillation with diffuse hyperplastic goiter was 47.7 years and for those with adenomatous goiter was fifty years.

The patients with adenomatous goiters had been aware of their presence for an average of 14.5 years, while 60 per cent of those with diffuse hyperplasia were unaware of any thyroid enlargement. The other 40 per cent had known of a goiter for from three months to twenty years, and the average duration had been 2.8 years. The average estimated duration of hyperthyroidism in those patients with diffuse hyperplasia with auricular fibrillation was 2.5 years and in those with adenomatous goiter 2.3 years. This is in contrast with eight months and twelve months respectively in those with normal rhythm. Auricular fibrillation was present in several patients who appeared to have had hyperthyroidism for only one month.

Some form of focal infection was present in 50 per cent of those with auricular fibrillation, and in 32 per cent of those without fibrillation. Syphilis occurred in 1.7 per cent of the patients with fibrillation.

Signs of congestive failure were present in only 3.2 per cent of those with normal rhythm as compared with 30 to 60 per cent (different series) of those with auricular fibrillation. An enlarged heart as shown by roentgen ray was present in only 6 per cent of those with normal rhythm and in each instance was associated with a diastolic blood pressure of 100 or more. On the other hand, in 60 per cent of those with auricular fibrillation roentgenograms revealed enlarged hearts and only 8 per cent of these had a diastolic blood pressure higher than 100. There was a systolic murmur at the apex of the heart in 60 per cent of those with

TABLE I
THYROIDECTOMY AND QUINIDINE IN THE TREATMENT OF PATIENTS WITH AURICULAR FIBRILLATION

	75 SERIES 1	75 SERIES 2	185 SERIES 3	57 SERIES 4	34 SERIES 5
Regular after thy- roidectomy	24 32%	45 60%	112 60.5%	26 45.7%	17 50%
Irregular after thyroidectomy	51 68%	30 40%	73 39.5%	31 54.3%	17 50%
Not treated with quinidine			57	7	0
Treated with quinidine		Late 3	Late 16	Prompt 23	Prompt 17
Regular after quinidine		2 66%	10 60%	22 96%	14 82%
Irregular after quinidine		1	6 40%	1 4%	3 18%
Regular after thy- roidectomy and quinidine			122 66%	48 85.96%	31 91%

normal rhythm and in 46 per cent of those with auricular fibrillation. There was an associated mitral stenosis in 3 per cent of these cases.

The first series I reported included 75 surgical patients who had had a persistent auricular fibrillation; 60 per cent of the series showed heart failure, and in 20 per cent this had progressed so far that general anasarca was present. In spite of this complication, 97 per cent improved enough for ligation or lobectomy to be attempted. In 60 per cent of this group ligations preceded thyroidectomy. The mortality in this series was 15 per cent, and only 32 per cent acquired a normal heart rhythm after operation.

Quinidine was used in the treatment of three patients in this first series and was successful in two. Of those who continued to have fibrillation postoperatively, 55 per cent were very comfortable and able to lead active lives, and 45 per cent were forced to restrict their activities considerably. However, some of this restriction was necessary on account of other factors, such as arthritis or arteriosclerosis.

The average age for this first series was fifty-one years. In none of the patients in this group was the fibrillation transient; in many of them it had been present for years. The maximum duration was twenty years. This series does not, therefore, represent a true picture of auricular fibrillation in general, but does show the seriousness of long standing cases.

A second series of seventy-five patients subjected to operation on the thyroid included all who showed a definite fibrillation. In five patients this was transient, lasting from a few hours to a few days. Ten gave a history of paroxysmal attacks over a long period of time, and in sixty, there had been continuous fibrillation.

The average age of the patients in this series was forty-seven years, and the mortality after operation was 4 per cent. All in this series were operated upon after preoperative iodine therapy became a routine procedure.

Some degree of heart failure was present in 55 per cent of these cases. This was slight in 20 per cent, moderate in 20 per cent, and advanced in 15 per cent. Normal rhythm was established postoperatively in 60 per cent. Quinidine was used in six cases but was successful only in three.

In a third series of 185 cases, 60 per cent of the patients showed a normal rhythm following thyroidectomy. Sixteen patients in whom fibrillation persisted were given quinidine; of these, in ten a normal rhythm was reestablished. Of the entire group, the total number of cases in which normal rhythm was regained was 66 per cent:

Before 1929 quinidine had not been used until one week after operation as it had been felt that there would be more attendant danger. Also there were some patients who did not develop a spontaneous normal rhythm until one to four weeks after operation. However, by this time sufficient study had been made to establish the fact that not more than

60 per cent of patients would acquire a normal rhythm with thyroidectomy alone, and also that quinidine used late (two to three weeks after operation) would only raise this figure slightly. The patients usually left the hospital on the sixth or seventh day following thyroidectomy and were seldom accessible for treatment afterward. Only approximately 20 per cent were treated with quinidine on this basis.

In 1930 prompt quinidine therapy was made routine treatment. That is, all patients still having auricular fibrillation on the third day after operation were reported. They were given a test dose of quinidine that evening, and if no ill effects were encountered, they were started on the regular schedule the morning of the fourth day. This included 5 grains of quinidine sulphate every four hours, day and night for twenty-four hours, every three hours for the next twenty-four hours, and every two hours for the next forty-eight hours. The pulse was counted before each dose, and if it was regular no more of the drug was administered.

It was found that only 45 per cent of the patients had acquired a normal rhythm by the end of the third postoperative day. According to the earlier results, this means that 15 per cent of patients might be expected to acquire a spontaneous rhythm if allowed to go on without taking quinidine, but I know of no way to determine which patients would make this recovery.

During 1930 there were fifty-seven patients with auricular fibrillation who had complete thyroidectomy. Twenty-six, 45.7 per cent, developed a normal heart rhythm within three or four days following thyroidectomy without any quinidine. Of the remaining thirty-one patients, two died, making a mortality in the series of 3.5 per cent. Seven were unintentionally not treated with quinidine and continued to have auricular fibrillation. Twenty-three received quinidine according to the schedule outlined previously. Twenty-two of these, or 96 per cent, acquired a normal rhythm and one did not. This patient after her third dose of quinidine became dyspneic, flushed, nauseated, she perspired and experienced fear of death. Whether this was a quinidine reaction or pulmonary embolus could not be determined, but the patient refused further treatment and the fibrillation persisted.

During the study of this series no attention was paid to the rate of the heart or to the extent of digitalization, and I have not observed that complete digitalization prior to quinidine therapy offered any advantage in treatment. So far as I know, no patient in this series has had recurrence of the auricular fibrillation while under observation or afterward, and in no instance has the use of quinidine been continued after the establishment of normal rhythm.

During 1931 there were thirty-four patients with auricular fibrillation who had complete thyroidectomy. Seventeen of these, or 50 per cent, developed a normal rhythm without taking any quinidine.

Quinidine was used according to the regimen already outlined in

seventeen patients; the treatment was successful in fourteen, and unsuccessful in three. Thus, in the entire series, 91 per cent of the patients had a normal heart rhythm at the time they left the hospital and three patients or 9 per cent still had auricular fibrillation when they were dismissed. There were no deaths in this series. One of these three patients did not have a full course as he wished to get home as soon as possible, and the other two patients had had recurrent hyperthyroidism.

The results of treatment with quinidine were not quite so satisfactory in the 1931 series as in the 1930 series, but show that one can expect 90 per cent or more of all patients to acquire a normal rhythm if treated with quinidine shortly after operation. The ideal time for instituting the administration of quinidine is from the third to the sixth postoperative day. If treatment is postponed later than this, the percentage of failures increases considerably.

The question is frequently asked, "Will not these patients again develop auricular fibrillation under any stress?" I am sure the answer is "No." I have only very occasional reports of a patient who has developed a subsequent auricular fibrillation that has not been due to a recurrent hyperthyroidism, and will refer to one patient who illustrates very well how stable the heart may be. This patient was treated with quinidine and on the third day she developed a normal rhythm. A few months later she was operated upon for the removal of a large fibroid, which was followed by general peritonitis which caused her death. For several days the temperature had varied between 103° and 105.5°, and the pulse rate ranged from 130 to 160, but at no time was there any irregularity of the heart action.

One patient developed a recurrent auricular fibrillation while taking thyroid extract. She was forty-six years of age, and symptoms of hyperthyroidism had been present for two years before thyroidectomy. After operation she continued to be nervous, and had a basal metabolic rate of plus 23 per cent. She continued to have auricular fibrillation which digitalis did not completely control, though it did slow the ventricular rate from 130 to 100, per minute. It certainly appeared that this patient had a residual hyperthyroidism, but there was no thyroid tissue palpable. A course of Lugol's solution was given which did not affect the heart. She was then given quinidine and acquired a normal heart rhythm. With that her nervousness and other symptoms disappeared and she returned to work. About a year later she had a dry skin, was rather drowsy, and had other symptoms of hypothyroidism and was given thyroid extract. During its administration she developed auricular fibrillation which lasted about two weeks and stopped spontaneously.

One patient who had only a lobectomy was given quinidine on the fourth day after operation and acquired normal heart rhythm, but the next day auricular fibrillation reappeared. In my experience with quinidine therapy this case was analogous to those seen before the hyper-

thyroidism had been controlled by thyroidectomy. In cases where insufficient thyroid tissue is removed the rhythm may become normal after operation but seldom lasts permanently. No routine attempt has been made to produce a normal heart rhythm by the use of quinidine before operation, as this seldom persists, and the presence of auricular fibrillation with good compensation seems to be no contraindication to operation.

SUMMARY AND CONCLUSIONS

The presence of auricular fibrillation in patients with hyperthyroidism seems to depend on two factors: first, duration of symptoms, and second, the severity of the condition.

The mortality in such cases has been reduced greatly by the routine use of iodine before operation.

Approximately 45 per cent of patients acquire a normal rhythm within four days after thyroidectomy, and about 15 per cent more would develop a normal rhythm if allowed to go untreated, but there is no way of knowing which ones they would be.

The remaining 40 per cent would continue to have an abnormal rhythm indefinitely if not treated with quinidine.

In order to obtain the optimum results with quinidine, it must be used from the third to the sixth day following thyroidectomy, and success can be anticipated in from 90 to 96 per cent of the cases. If treatment is delayed longer than this, the percentage of failures increases considerably.

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(For discussion, see page 154.)

STUDIES IN THYROID HEART DISEASE*

THE VALUE OF ERGOTAMINE IN HYPERTHYROIDISM AND ITS EFFECT ON THE ELECTROCARDIOGRAM

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THIS report is a clinical one and represents our experience and impression as to the use or value of ergotamine in hyperthyroidism, and the influence of ergotamine on the human electrocardiogram in these cases. Our interest in this drug was aroused by the relatively numerous reports of its use in hyperthyroidism abroad and because the drug was being increasingly recommended to the American physician by its manufacturer for use in similar cases. Accordingly, we were able to obtain a supply of the drug from the Sandoz Company for our studies.

The use of ergot in hyperthyroidism is not a new thing. Nearly twenty years ago Forchheimer¹ reported that he had used a combination of quinin and ergotin over a period of many years in Graves' disease. Forchheimer observed improvement in the tachycardia, tremor, and decrease in size of the thyroid gland under this treatment. In addition to stating that he obtained a great percentage of complete recoveries, he also recommended the use of quinin-ergotin as a pre-operative measure to get the patients in condition for surgery.

About 10 years ago, Stoll² isolated the principal alkaloid of ergot. This was called ergotamine tartrate at the time but later came to be known also as gynergen. The two terms will be used here interchangeably. After its isolation, ergotamine came to be extensively used in place of ergot, as the former lacked some of the drawbacks of ergot itself. Today ergotamine or gynergen is supplied in tablets of 1 mg. each for oral administration and in ampules of 1/2 mg. each for hypodermic and intravenous use. Because it is generally recognized that there is an associated increased activity of the sympathetics in Basedow's disease, the use of ergot and ergotamine, which is known to have, or is thought to have, a depressing action on the sympathetics, naturally suggested itself as a means of relief. Accordingly, we find that ergotamine has been widely used in some European countries for this purpose. In our country, apparently, the drug has been relatively little used in goiter cases, judging from the scarcity of reports in the literature.

Among the earliest reports on the use of gynergen in hyperthyroidism is that of Adlersberg and Porges³ published in 1924. They report a series of 22 cases treated over a period of one and one-half years. They

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gave the drug subcutaneously 0.5 c.c. to 1 c.c. twice daily over a period of 1 to 3 weeks and then a week's period of rest. These authors divide their case results into three groups. Group I, consisting of 15 cases showing marked improvement subjectively and objectively, in tremor, tachycardia, exophthalmos, weight curve and basal metabolic rate. Group II, 4 cases with moderate improvement, and 3 cases in Group III showing no appreciable improvement. Their experience was that in the improved cases, recurrences took place 8 to 12 weeks after ergotamine was stopped, so that the medication had to be resumed with the reappearance of symptoms. They concluded at the time that ergotamine did not constitute a cure. In a latter follow-up report⁴ of 13 of these 22 patients, they report nearly complete cure of the cases.

Marine⁵ and his associates employed ergotamine to evaluate its effect on the heat production of normal and thyroidectomized rabbits. They employed the drug in doses of $\frac{1}{8}$, $\frac{1}{4}$, and $\frac{1}{2}$ mg. subcutaneously, using 0.9 per cent saline solution subcutaneously for control purposes. They report a striking fall in the heat production within one hour, the fall being proportional to the amount of ergotamine used. After thyroidectomy, employing $\frac{1}{4}$ mg. ergotamine in these rabbits, the heat production was again found lowered but to a less extent than in normal animals.

Youmans and Trimble,⁶ who probably have done more work with ergotamine than anybody else in the country, used 0.25 mg. intravenously in normal trained dogs to test the effect of ergotamine on the oxygen consumption. They found that only 2 dogs showed a slight decrease in the O_2 consumption in the first hourly period while nearly all the others showed a rise, greatest usually in the first hour and decreasing to almost level limits at the end of the third hour. The giving of atropine (0.3 mg. or 0.4 mg.) before or after ergotamine injection did not influence the effect of gynergen on the oxygen consumption.

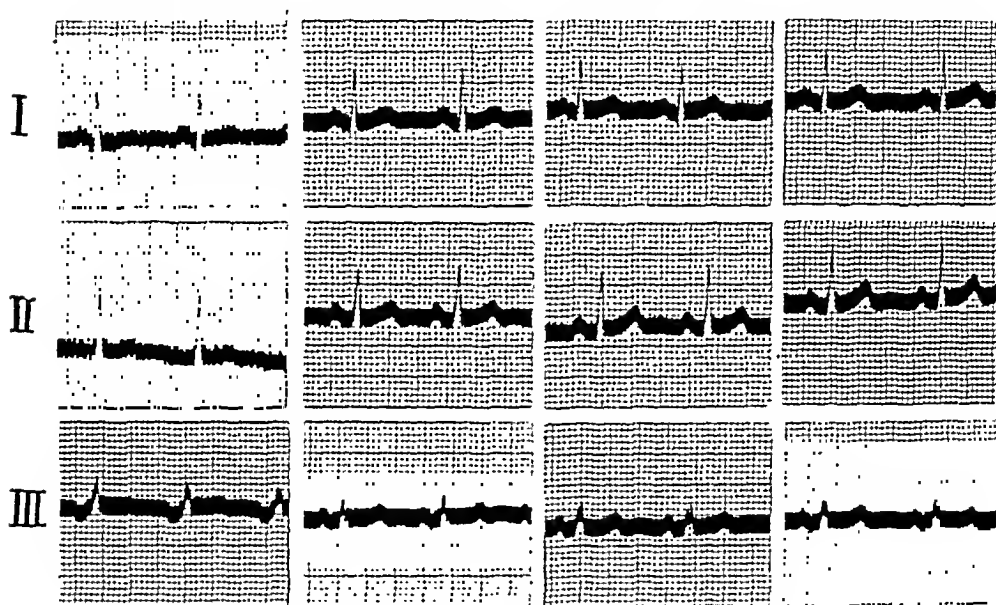
Employing nine normal human subjects, Youmans and Trimble⁷ used 0.5 mg. ergotamine subcutaneously to test the effect of the drug on the basal metabolism. They found a slight elevation of the basal metabolic rate in three subjects at the end of three hours, while the others showed a variable drop (maximum 9 per cent) at some time after the injection but no greater variation than seen in control readings over the same period of time. In another series of 3 patients (normals) they gave 1 mg. ergotamine t.i.d. over a period of 8 days and found no change in the basal metabolic rates.

The same workers⁸ in determining the effect of ergotamine on the heart rate in normal dogs employed 0.25 to 0.5 mg. of the drug intravenously. They found this to cause a sudden and marked slowing of the heart. Injection of 0.05 mg. atropine per Kg. entirely abolished this effect of ergotamine in slowing the heart. They concluded that ergotamine therefore produced its slowing action by a sensitizing or stimulating action on the vagus mechanism. In dogs with vagi cut, however, the injection of ergotamine still caused a slowing of the heart

but relatively much less than in intact dogs. During the course of this particular experiment, electrocardiographic studies showed no changes aside from slowing of the sinus rhythm.

In 1928, Merke and Eisner⁹ employed gynergen to determine its effect on the human electrocardiogram in Basedow's disease. Using 1 c.c.

Control	10 min. after inj.	20 min. after inj.	30 min. after inj.
Rate 83	1cc. Ergotamine	Rate 79	Rate 73
P-R 0.16	Rate 100	Complexes	P-R 0.16
P ₃ inverted	P+T better def.	same	Compare P+T
B. P $\frac{128}{80}$	B. P $\frac{120}{80}$	B. P $\frac{120}{80}$	B. P $\frac{118}{78}$



Mrs B K (B 37393) Non-toxic Adenoma of Thyroid
with Pressure Symptoms

gynergen intramuscularly in a series of cases and taking curves 10 and 20 minutes after injection they found the following:

P-R interval prolonged.

R-R interval prolonged.

P-wave decreased in height in nearly all instances.

T-wave decreased in majority of cases.

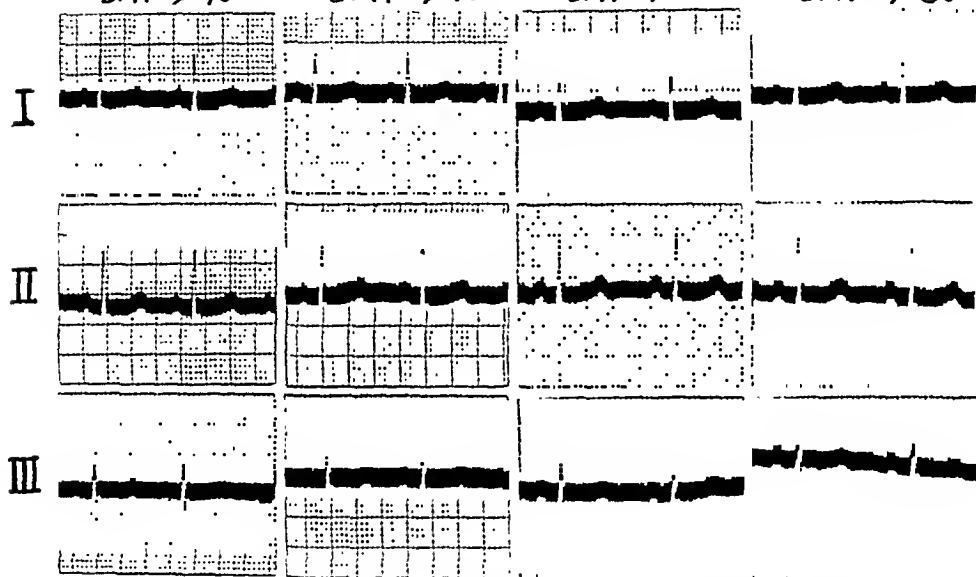
R-wave decreased in majority of cases.

PERSONAL EXPERIENCES

Our series consists of six patients, 5 females and 1 male ranging in age from thirty-one to sixty-four years. Five of these had thyrotoxicosis of various degree and severity. The sixth had a nontoxic adenoma with pressure symptoms. Four of our group were given ergotamine

orally or hypodermically over different periods of time and their general, as well as their metabolic, response was noted. All six patients were given also 1 c.c. (0.5 mg.) of ergotamine subcutaneously and the changes in the electrocardiogram noted at approximately ten, twenty, and thirty-minute intervals after the injection.

Control	5 min. after inj	16 min. after inj.	31 min. after inj.
P-R 0.16	1cc. Ergotamine	Rate 71	Rate 75
Rate 83	Rate 76	P ₂ P ₃ T ₂ & T ₃	Complexes
	T ₃ increased	better defined	Same
		than control.	P-R 0.16
B. P. 124/70	B. P. 134/70	B. P. 138/72	B. P. 142/80



Mrs. P. S. (B35433) Adenoma with Hyperthyroidism

CASE REPORTS*

CASE 1.—Mrs. M. B. (B36701), thirty-five years old; diagnosis exophthalmic goiter.

Metabolic Studies

Date	B. M. R.	Pulse	Remarks
4/14/31	+39.	80 80	No medication. First Reading.
4/17/31	+34.1	80	No medication.
4/22/31	+28.7	80	After receiving gynergen ½ c.c. "H" B.I.D. since 4/17/31.
4/29/31	+19.1	84	Gynergen ½ c.c. B.I.D. plus gynergen tab. q.i.d. since 4/22/31.
5/ 1/31	+13.6	84	Gynergen ½ c.c. B.I.D. plus gynergen tab. q.i.d. since 4/22/31.
5/ 6/31	Thyroidectomy		On Lugol's m. x t.i.d. since 5/1/31.
5/12/31	+21.5	88	

*Details of four of the six cases studied are given here.

CASE 2.—Mrs. P. S. (35433), married, aged forty-six years; diagnosis exophthalmic goiter; diabetes mellitus.

<i>Date</i>	<i>B. M. R.</i>	<i>Pulse</i>	<i>Remarks</i>
3/ 9/31	+43.2	78	No medication. First reading.
3/10/31	+26.2	72	No medication.
3/12/31	+25.6	76	Insulin therapy started.
3/18/31	+31.4	72	No medication except insulin.
3/23/31	+24.9	74	No medication except insulin.
3/25/31	+33.9	72	No medication except insulin.
3/28/31	+34.8	82	No medication except insulin.
4/ 7/31	+28.4	72	Lugol's m. × t.i.d. and ergotamine $\frac{1}{2}$ c.c. B.I.D. started 4/2/31.
4/13/31	+15.9	68	On Lugol's and ergotamine since 4/2/31.
4/16/31			Subtotal thyroidectomy.
4/22/31	+ 2.5	68	One week after thyroidectomy.

CASE 3.—Mrs. A. C. (B35604), married, aged forty-five years; diagnosis adenomatous goiter with hyperthyroidism; mitral insufficiency; diabetes mellitus.

<i>Date</i>	<i>B. M. R.</i>	<i>Pulse</i>	<i>Remarks</i>
3/12/31	+62.7	100	No medication, first reading, not satisfactory.
3/16/31	+43.1	88	No medication.
3/18/31	+39.8	84	No medication.
3/23/31	+51.	76	No medication.
3/25/31	+46.8	72	No medication.
3/28/31	+52.5	68	No medication.
4/ 7/31	+46.9	80	On ergotamine $\frac{1}{2}$ c.c. B.I.D. since 4/3/31.
4/13/31	+55.7	78	On ergotamine $\frac{1}{2}$ c.c. B.I.D. since 4/3/31 and continued to 4/16/31 inc.
4/17/31	+40.9	92	On Lugol's m. × t.i.d. and Tab. ergotamine t.i.d. since 4/14/31.
4/22/31	+32.5	84	On Lugol's m. × t.i.d. (Gynergen tablet stopped 4/20/31.)
4/27/31	+45.9	100	On Lugol's m. × t.i.d.
5/ 5/31	+50.3	88	On Lugol's m. × t.i.d.
5/ 8/31	+ 9.3	80	On Lugol's m. × t.i.d.
5/11/31	+10.1	80	On Lugol's m. × t.i.d.
5/13/31			Thyroidectomy.
5/19/31	+18.7		

CASE 4.—Mrs. L. L. (B36257), widow, sixty-four years old; diagnosis recurrent thyrotoxicosis; bleeding duodenal ulcer; generalized arteriosclerosis; arteriosclerotic heart; cardiac hypertrophy; mitral insufficiency.

<i>Date</i>	<i>B. M. R.</i>	<i>Pulse</i>	<i>Remarks</i>
4/ 6/31	+30.8	96	No medication.
4/13/31	+40.6	84	No medication.
4/ 2/31	+30.7	72	Patient received 4 injections of $\frac{1}{2}$ c.c. ergotamine between April 17 and 19. Drug discontinued when patient complained of marked palpitation, nervousness and severe abdominal pains and cramps.
5/ 2/31	+36.7	80	On Blaud's mass.
5/12/31	+30.2	76	On Lugol's m. × t.i.d. p.c. from May 3 to 7 when further Lugol's was refused by the patient.

We wish to state here that we realize that the number of our case determinations are relatively few owing to conditions at the time beyond

our control. During the course of administration of ergotamine, all but one case, with a complicating recurrent bleeding duodenal ulcer, stated they were improved. This improvement consisted of lessened nervousness and irritability, decreased palpitation, decreased tachycardia, and a feeling of increased strength. It must of course be realized that these patients were all at complete bed rest during this time and due account of this factor must be taken into consideration in evaluation of this drug as well as any other under similar conditions. However, we feel that too much stress or value should not be placed on the bed resting phase as being in a large medical ward among the sick, ailing and complaining patients cannot be said to be very conducive to the improvement or recovery of a thyrotoxic patient. No ergot poisoning was experienced in our series.

Incidentally during this time we employed ergotamine in a case of paroxysmal tachycardia of nonthyroid origin, which failed to respond to the usual measures for relief, and which was controlled by the subcutaneous injection of the drug. In another case of tachycardia in an old rheumatic heart, the heart rate was not slowed after the oral administration of gynergen—one tablet 3 times daily over a period of 3 to 4 weeks. In still another case of tachycardia of unknown source and without any other cardiac involvement and without evidence of hyperthyroidism, slowing of the heart rate was not obtained after several weeks of the drug by mouth. This is rather interesting in view of the slowing of the heart rate in goiter cases.

The electrocardiographic responses to ergotamine are more interesting and definite. After a control electrocardiogram, pulse rate, and blood pressure determinations, serial electrocardiograms were taken at approximately 10, 20 and 30 minute intervals following the subcutaneous injection of 1 c.c. gynergen. In addition, pulse rate and blood pressure readings were made every few minutes during this half hour period of observation. Likewise any new subjective symptoms which the patient experienced during this period were recorded. The electrocardiographic changes occur rather promptly and consist chiefly of a slowing of the heart rate, increased amplitude of the T-wave in most instances and particularly in Lead III, and the abolishing of the peripheral tremors present in some cases in the control electrocardiogram. The P-wave was increased in three cases, and decreased in two. In one case of thyrotoxicosis and auricular fibrillation, the electrocardiogram showed no changes in the complexes after the administration of ergotamine subcutaneously. The P-R interval was increased in two cases, and unchanged in the others.

The cause or causes for the P- and T-wave changes in this series offer an interesting field for speculation. The increase in the T-wave after the employment of a drug supposedly beneficial in hyperthyroidism is further very interesting in view of the report of a decrease in the T-wave under iodine medication and after thyroidectomy as reported previously

by ourselves.¹⁰ It is to be noted here also, that the greatest changes occur in the third lead, which lead has always been considered as the most sensitive and labile of the three leads.

SUMMARY AND CONCLUSIONS

1. Four patients with hyperthyroidism, were given ergotamine orally or hypodermically. One case showed an increased basal metabolic rate after 10 days; one showed a decrease in 14 days, one a decrease in 2 days, and the fourth case in which Lingol's had been combined with ergotamine a decrease in 11 days.

2. As a result of our experience we conclude that ergotamine, in the dosage and mode of administration employed is not as effective as Lingol's solution in reducing the basal metabolic rate. Neither do we feel that the drug can be called a "cure" for thyrotoxicosis. It does contribute to the subjective improvement of the patient but no more than does the use of Lingol's solution.

3. The tachycardia of hyperthyroidism is generally favorably influenced by ergotamine. The same drug when used in two cases of tachycardia not of thyroid origin, failed to produce a slowing of the heart rate.

4. Subcutaneous injection of ergotamine in the majority of instances causes a fairly prompt change in the electrocardiogram, consisting chiefly of a slowing of the heart rate and an increase in height of the T-wave. In two of the six patients it produced a prolongation of the P-R interval. It likewise causes in most cases of hyperthyroidism an increase in the systolic and diastolic blood pressure, persisting at least one-half hour after its administration.

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(For discussion, see page 134.)

Society Transactions

AMERICAN HEART ASSOCIATION, 1932

THE eighth annual scientific session of the American Heart Association was held at the Roosevelt Hotel, New Orleans, La., on May 10, 1932, with Dr. Harold E. B. Pardee as the presiding officer.

DR. PARDEE.—Today's presentation represents the second attempt on the part of the Committee for the Coordination of Investigation* to provide a comprehensive study of various phases of cardiovascular disease. By way of introduction to this symposium, it seems proper to point out the objectives which the Committee had in mind when selecting the subject. It was hoped to present a fairly complete picture of the cardiac disturbances, both physiological and pathological, which result from an abnormal functioning of the thyroid gland. It was hoped also to focus attention upon those points which were in dispute and especially upon those which seemed most ready for solution.

In the past, studies of the pathological features of the hearts of those with thyroid disease have frequently been unsatisfactory because of the difficulty in deciding what was due to the direct influence of the gland and what to a complicating factor. First, the coincident presence of arteriosclerosis of the coronary arteries has been a great source of confusion, and it seems that changes due to this have often been wrongly considered as an effect of thyroid disease. Second, auricular fibrillation, from its tendency to produce a rapid heart rate, can give rise to cardiac insufficiency and this in its turn to cardiac enlargement of myocardial fibrosis or possibly other changes. Obviously if such abnormalities result from heart failure, they cannot properly be considered as an effect of thyroid dysfunction upon the heart. It has been suggested that the prolonged cardiac overactivity which is known to result from hyperthyroidism might give rise to premature coronary arteriosclerosis, and it was hoped that we might be able to reach a decision as to whether or not such premature sclerosis occurs.

There has been no doubt but that thyroid disturbances lead to disturbances of cardiac function. The rate and rhythm of the heart and the blood pressure are evidently affected, but it is not yet definitely established whether the cardiac functional capacity is diminished by the uncomplicated influence of thyroid dysfunction. Auricular fibrillation, if permanent and associated with a rapid ventricular rate, is quite capable of causing serious cardiac insufficiency. The arteriosclerotic changes in the coronary arteries which appear normally after the fourth decade can also give rise to cardiac insufficiency. It is difficult in a patient who has either of these complicating conditions clearly to discern the influence of thyroid dysfunction upon the heart. We must try to separate the influence of the thyroid from whichever of these complications may be present, or better yet to select for study cases from which both can be excluded.

On the experimental side there is much to be learned about the effects upon the heart's function and structure produced by the administration of thyroxin and of thyroid gland. The heart after thyroidectomy has been little studied, either as to functional or structural changes. Finally the question of the influence of a simple nontoxic adenoma should be settled. Does this condition cause physiological and

*Edward P. Carter, Cary Eggleston, George R. Herrmann, William J. Kerr, Edward B. Krumhaar, H. M. Marvin, Fred M. Smith, Paul D. White, Frank N. Wilson, Harold E. B. Pardee, Chairman.

pathological changes in the heart such as have been associated with under- or over-activity of the thyroid, or does it not? Each one of the contributors to this symposium has attempted to answer one or more of these questions and to investigate such other phases of the subject as have seemed important to them. From my preliminary correspondence with the authors who will address you today, I feel quite certain that by the end of this program they will have presented us with a much clearer picture of thyroid heart disease than exists at present.

The papers comprising the program of the meeting are published in this issue.

PROGRAM

The Mechanism of Adjustment of the Circulation in Hyperthyroidism (Thyrotoxicosis). Wallace M. Yater, M.D., Washington, D. C. (See p. 1.)

Cardiac Histopathology in Thyroid Disease. Carl V. Weller, M.D., R. C. Wanstrom, M.D., Harold Gordon, M.D., and J. C. Bugher, M.D., Ann Arbor, Mich. (See p. 8.)

A Study of the Heart in Hyperthyroidism. Geoffrey Rake, M.B., and Donald McEachern, M.D., Baltimore, Md. (See p. 19.)

The Signs and Symptoms of Heart Changes in Toxic Goiter. A Clinical Study of 148 Cases. Clough Turrill Burnett, M.D., and Edgar Durbin, M.D., Denver, Colo. (See p. 29.)

Cardiovascular Symptomatology in Exophthalmic Goiter. Jacob Lerman, M.D., and J. H. Means, M.D., Boston, Mass. (See p. 55.)

The Heart in Hyperthyroidism. E. Cowles Andrus, M.D., Baltimore, Md. (See p. 66.)

Cardiac Status After Prolonged Thyrotoxicosis. J. Marion Read, M.D., San Francisco, Cal. (See p. 84.)

Myxedema Heart. George Fahr, M.D., Minneapolis, Minn. (See p. 91.)

Congestive Heart Failure and Hypertrophy in Hyperthyroidism: A Clinical and Pathological Study of 178 Fatal Cases. E. J. Kepler, M.D., and A. R. Barnes, M.D., Rochester, Minn. (See p. 102.)

Studies in Thyroid Heart Disease, Angina Pectoris and Hyperthyroidism. Morris W. Lev, M.D., and Walter W. Hamburger, M.D., Chicago, Ill. (See p. 109.)

Experimental Observations Upon Hearts of Thyroxinized Animals. E. Cowles Andrus, M.D., and Donald McEachern, M.D., Baltimore, Md.

The Influence of Thyroid Extract and Hyperthyroidism on the Electrocardiogram, With Special Reference to the T-Waves. Johnson McGuire, M.D., and Margaret Foulger, M.D., Cincinnati, Ohio. (See p. 114.)

Cardiac Dilatation in Toxic Goiter: A Study of the Changes in the Size and Shape of the Heart Before and After Treatment. O. J. Menard, M.D., and Lewis M. Hurxthal, M.D., Boston, Mass.

ABSTRACT

Teleroentgenograms were made in one hundred and fifteen cases of toxic goiter, before, during, and after treatment. Comparisons of the films were made by superimposing one plate upon another. Changes in the chest, diaphragm, and so forth were given due consideration in deciding upon changes in heart size. Marked reduction in the size of the heart shadow was found after treatment, particularly in cases with auricular fibrillation and congestive failure. Relief of congestive failure alone caused a reduction in the size of the shadow, while a change from auricular fibrillation to normal rhythm produced a reduction in size in some cases.

The heart shadow became smaller after operation in a few cases with normal rhythm and without evidence of congestive failure. In about 50 per cent of those with normal rhythm and with evidence of congestive failure, there was a smaller shadow after relief of hyperthyroidism. Larger heart shadows after treatment were seen in a few cases and these were usually associated with coincident heart disease, excessive gain in weight, or occasionally unknown causes.

The shape of the heart was studied, and a prominence of the pulmonary artery was noted more particularly in toxic goiter cases than in nontoxic goiter cases. Slight to moderate degrees of ventricular hypertrophy were found particularly in cases of long duration, but gross cardiac enlargement was usually associated with coincident cardiovascular disease.

Auricular Fibrillation in Graves' Disease. Paul S. Barker, M.D.; Anne L. Bohning, M.D.; and Frank N. Wilson, M.D.; Ann Arbor, Mich. (See p. 121.)

The Incidence of Auricular Fibrillation and Results of Quinidine Therapy. John P. Anderson, M.D., Cleveland, Ohio. (See p. 128.)

The Value of Ergotamine in Hyperthyroidism and Its Effect on the Electrocardiogram. Morris W. Lev, M.D., and Walter W. Hamburger, M.D., Chicago, Ill. (See p. 134.)

READ BY TITLE

The Heart in Hyperthyroidism: An Experimental Study. Frank R. Menne, M.D.; Roger H. Keane, A.B.; Robert T. Henry, A.B.; and Noble W. Jones, M.D., Portland, Ore. (See p. 75.)

A Clinical Study of Goiter in the Pacific Northwest, With Special Reference to the State of the Heart. Noble W. Jones, M.D., Dean B. Senbrook, M.D., and Frank R. Menne, M.D., Portland, Ore. (See p. 41.)

The Heart Rate During Sleep in Graves' Disease and in Neurogenic Sinus Tachycardia. Ernst P. Boas, M.D., New York, N. Y. (See p. 24.)

The Heart in Thyroid Disease: Electrocardiographic and Orthodiagraphic Studies Before and After Thyroidectomy. Edward Rose, M.D.; Alexander Margolies, M.D.; and Francis C. Wood, M.D., Philadelphia, Pa.

(A preliminary report of this paper was read by title at the New Orleans meeting. The final report will be published later.)

DISCUSSION

Discussion of paper of Dr. Wallace M. Yater. (See p. 1.)

Dr. John J. Sampson, San Francisco, Calif.—There is additional evidence on this subject which was presented by J. K. Lewis and W. Dock, published in the *Journal of Physiology*, April issue of this year. Their work was designed to show the direct influence of thyroxin on the metabolism of heart muscle. They used a rat heart-lung preparation to determine the metabolism of the heart muscle in a normal animal and in an animal thyroxinized. They found that the direct measurement of the metabolism of the heart muscle was no greater than would be expected from the increased rate. The action of the thyroxin, they stated, is to increase the heart rate, and no increase in metabolism of the heart muscle occurred, greater than expected per gram per beat.

Discussion of paper of Drs. Carl V. Weller, R. C. Wanstrom, J. C. Bugher, and H. Gordon. (See p. 8.)

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask Dr. Bugher if there were any special clinical features about the cases in which special pathological findings were observed, especially if cardiac insufficiency was present.

Dr. John J. Sampson, San Francisco, Calif.—Did the studies carried out at autopsy reveal anything peculiar in other organs than the heart, especially pancreas, kidney or skeletal muscles?

Dr. Wallace M. Yater, Washington, D. C.—A similar change is seen in rabbit hearts. Rabbits which have been injected with thyroxin are more susceptible to infection and also show unusual lesions after chloroform poisoning. They very readily develop focal necrosis throughout the heart and other lesions, which indicates that the myocardium in hyperthyroidism is less able than normally to cope with infection and poisons.

Dr. J. C. Bugher, Ann Arbor, Mich.—With regard to the special clinical features, the majority of these cases died primarily of pneumonia and other infections. In the exophthalmic goiter series, about the same number. Two-thirds of the cases of the combined exophthalmic goiter and adenomatous goiter series died with an attendant purulent infection of some kind, such as pneumonia or appendicitis. A number of them had tuberculous. In general, a very complex and very far-reaching picture was presented from the standpoint of the full pathology of the cases.

Several of the deaths were ascribed to myocardial failure. Since the series goes back as far as 1896, it is possible that if these were diagnosed in the light of present knowledge, there might be changes in that opinion.

Of the seven cases showing cellular infiltrations in the myocardium, four had had auricular fibrillation and died of myocardial failure; another one of the earlier cases died of "acute cardiac dilatation"; a sixth died of cardiac failure in a thyroid crisis; the last case was one of lymphatic leucemia with the exophthalmic goiter secondary in importance. The four cases in which the cellular infiltrations were chiefly epicardial included two with auricular fibrillation, one of which died of myocardial failure.

With regard to the involvement of other organs in these cases, the chief organ involvement in the exophthalmic goiter series was the liver. Dr. Weller has reported the rather high incidence of what appears to be a nonspecific hepatitis in which there is heavy round-cell infiltration associated with some fibroblastic proliferation.

The other organs do not appear to show such distinctive inflammatory infiltrations, but there is very constantly in these exophthalmic goiter cases and in most of the adenomatous goiter individuals a hypoplastic cardiovascular state, associated with a hyperplastic lymphoid tissue.

The comment on the work on rabbits was very instructive. Goodpasture and a number of other workers have also called attention to this as a possible interpretation of such lesions occurring in the myocardium of human beings. We are not at all opposed to any such theory, although it does not necessarily follow from our investigative work. However, it is a reasonable interpretation of the association of these myocardial lesions with exophthalmic goiter.

Discussion of papers of Drs. Clough T. Burnett and Edgar Durbin (see p. 29); of Drs. Jacob Lerman and J. S. Means (see p. 55); and of Dr. E. Cowles Andrus (see p. 66).

Dr. George Herrmann, Galveston, Tex.—The point that Dr. Andrus made with relation to previous heart damage as a factor determining thyroid heart disease seems to be of some significance. Dr. J. A. Alvarez, who is studying the general heart condition at the Charity Hospital from 1926 to 1931, found himself in agreement with Dr. E. H. Schwab, who is studying the same question in Galveston. Both observed a considerable frequency and an early onset of heart complications in the thyrotoxic negro. In the study in Galveston it is striking that with a similar type of disorder the negroes have heart failure much earlier in life than do the whites. This observation is in line with some of Dr. Schwab's earlier studies which showed that the colored patient with hypertension developed heart failure earlier than did the

white. Dr. Schwab has suggested that the reason for the negro patient's earlier failure is the poor cardiovascular soil upon which the goiter reacts. He believes that the poor cardiovascular soil is a product of the recent civilization of the negro who has been forced to change his mode and especially his tempo of living. Dr. Schwab has gone back to the origin of the American negro and has found that the tendency to cardiovascular disease is not so great. At any rate in many of the negroes the age of thyroid heart disease is much under forty.

I wish to take issue with the statement of Dr. Lerman as to the possibility of carrying on with active exophthalmic goiter for many years without any cardiac manifestations. In my experience it is a distinct rarity for a patient with marked hyperthyroidism to have it for ten or twenty years without developing some organic myocardial disturbance. I still believe that the cardiac part of the exophthalmic goiter is a most important one and that the patient who has a perfectly normal myocardium before and after is quite an exception. We should have a statement as to the cause of death in the patients here considered to show the relative importance of cardiac failure in contrast to the other causes of death in these patients.

Dr. E. J. Kepler, Rochester, Minn.—I would like to ask Dr. Andrus if there were any patients in his series with congestive failure without persistent auricular fibrillation.

Dr. Louis F. Bishop, Jr., New York, N. Y.—I should like to call attention to the number of patients in whom Dr. Burnett found dizziness as a symptom. It is well known that a very rapid heart or a very slow heart may affect the blood supply to the brain with resultant dizziness, amounting in some cases to syncope. I was particularly interested to note that he found this symptom without any evidence of associated arteriosclerosis.

Dr. Wallace M. Yater, Washington, D. C.—This work is exceedingly interesting to me inasmuch as I have been doing the same kind of work independently of Dr. Andrus' group. He has worked in Baltimore and I have been working in Washington, only forty miles apart, and neither of us, apparently, was for a long time aware of the other's work. Our results have been practically identical in the main. The problems are multiple and difficult of solution. Of course, in the first place no one knows exactly what hyperthyroidism is. No one knows completely even what the function of the thyroid gland is. Why we should need a gland in the body to step our metabolism up 40 per cent is a mystery. When something happens to make the amount of thyroxin greater or less in the tissues, all tissues are affected in the same relative degree. The heart naturally is affected the same as other tissues of the body.

Theoretically what would be the effect of the increased rate of metabolism in the parenchyma of the only pulsating organ of the body? As I see it, there would be two main effects. First, there should be an increased irritability, which means tachycardia. The degree of tachycardia would depend mainly upon the amount of thyroxin in the myocardium, but would also depend to some extent upon the type of individual in whom the hyperthyroidism existed, whether sympatheticotonic or vagotonic, since there still exists a certain amount of nerve control. The other effect on the pulsating organ would be an increase in tone, with a corresponding increase in the force of the heartbeat. If the heart to begin with were hypotonic, there would be more increase in tone than in rate, a well known physiological principle. In either case, however, the resultant of these two main effects would be a considerable increase in minute volume output of the heart. Inasmuch as there is no physiological mechanism which controls the output of the heart in hyperthyroidism, the increased output is, therefore, largely a coincidence. It is easy for me to understand that the heart does more work than it normally should because it is a pulsating organ and in this condition lacks physiological control.

In regard to the work of Dr. McEachern with reference to the oxygen consump-

tion of strips of auricular muscle one should not place too much emphasis upon the results of this type of experiment, because such strips are doing practically no work.

In reference to the failure of the heart in hyperthyroidism, there are undoubtedly two main factors which act to bring about the failure. The first is age, with its natural diminution of cardiac reserve, and the second is general malnutrition, which naturally reduces the ability of any organ to carry on its work.

Dr. Harold E. B. Pardee, New York, N. Y.—I noticed there were some experiments which included observations of the effect of thyroid itself and also of thyroxin. I wonder if you have found any significant difference in the action of these two substances.

Dr. E. Cowles Andrus, Baltimore, Md.—All these animals received thyroxin or thyroid extract by mouth over relatively long periods of time, from ten days to two weeks. It is much easier to demonstrate the effect of thyroxin in this way than with the single large dose. It appears certain that thyroxin exerts no immediate effect in vitro. We were unable, in any experiments, to induce any significant reaction in isolated hearts by the addition of thyroxin directly to the perfusion fluid or to the bath in which the auricles were immersed. It is apparently true that noticeable reaction takes place only after a period of from twenty-four to thirty-six hours. After that the characteristic results appear and tend to persist for ten days to two weeks, unless the dose is repeated.

No quantitative differences were observed between the action of thyroxin and of thyroid gland substance.

Dr. Clough T. Burnett, Denver, Colo.—A question was asked as to the incidence of congestive heart failure and established auricular fibrillation. We found congestive heart failure in four cases in which there was no demonstrated fibrillation at any time. Negroes did not play a part in our series. I think there were only three in the entire group. I think perhaps the greatest trouble we had was in the determination of the duration of symptoms. How long have these patients had this trouble before they came in? How long has there been an effect on the heart? This is something which is sometimes very difficult to obtain in studying a record after six or seven years and with no contact with the patient.

Dr. Jacob Lerman, Boston, Mass.—As mentioned before, male patients complain very little. That, to us, is a prominent feature of the disease. These male patients may have had the disease for many years but do not come to the clinic until someone calls their attention to it.

Two years ago it was pointed out by Vanden Berg before the American Association for the Study of Goiter that patients often date the onset of their disease a year or less back, but that on questioning them after they are cured one finds their symptoms may actually date back ten or more years. Consequently the duration of the disease is difficult to determine.

Dr. E. Cowles Andrus, Baltimore, Md.—To answer the question concerning the incidence of fibrillation in connection with congestive failure, we had twenty cases in which there was normal rhythm and congestive failure, but many of those had paroxysms of fibrillation lasting from two to, in one case, sixteen hours. The duration of symptoms, I should agree, is very, very difficult to determine. I am prepared to believe that in the series we have reported it was greater, in the majority of instances, than was recorded.

Discussion of paper of Dr. George Fahr. (See p. 91.)

Dr. Jacob Lerman, Boston, Mass.—A week ago Dr. Means and I reported on a series of thirty patients with myxedema seen in Boston who had roentgen ray measurements of the heart taken before and after treatment. Our results are as follows: In fourteen cases the transverse diameter of the heart shrank 2 to 7 cm., and in six more it shrank 1 to 2 cm. The shrinkage of the heart was proportional to the

degree of enlargement. It is interesting to note that the time for the maximum shrinkage to take place was three to four months. Only one of the patients showed frank congestive failure.

Dr. J. Marion Read, San Francisco, Calif.—I should like to ask Dr. Fahr if he considers some other factor is operative to produce congestive failure in these patients with myxedema. I believe I can speak for most of those present that we frequently see myxedema patients even with metabolic rates as low as minus 30 who do not show evidence of myocardial decompensation. I have not yet seen a patient who fits Dr. Fahr's description of the "myxedema heart," although I have been looking for one ever since the publication of his first paper on this subject. I do not doubt that such a clinical picture exists, but I wonder if there isn't some complicating factor operating in these patients to produce the cardiac failure.

Dr. David W. Carter, Jr., Dallas, Tex.—I am surprised to hear Dr. Fahr say that there was only one patient in his series who developed anginal pain following treatment with thyroid substance. Our experience has been that it occurs more frequently than this in our series of patients of about the same age.

Dr. Bayard Holmes, Chicago, Ill.—The same condition prevails in beriberi. We see severe cases of beriberi with marked enlargement and dilatation of the heart, and as soon as they are put on a proper diet the size of the heart decreases just as with thyroid in these myxedema cases.

Dr. William D. Reid, Boston, Mass.—Did the abnormal electrocardiograms and roentgen findings always occur together, or sometimes was there a disagreement?

Dr. George Herrmann, Galveston, Tex.—I should like to ask Dr. Fahr what the relative hemoglobin concentration or the red blood cell counts showed in these hypothyroid cases that had the most extreme type of cardiac dilatation and edema and also what the blood serum protein levels were during the edema and after its disappearance.

Dr. Clough T. Burnett, Denver, Colo.—In the case of the anginal pain, did that pain appear before the reduction in the size of the heart?

Dr. E. J. Kepler, Rochester, Minn.—I would like to ask Dr. Fahr if an increase in the protein of the diet produced any change in the condition of the patients.

Dr. A. G. Sullivan, Hot Springs, Ark.—Did Dr. Fahr note the presence of arrhythmia in any of his cases; also does he believe that the increase in diameter of the cardiac shadow is due wholly to dilatation or may it not be due in part at least to a loss of cardiac muscle tone, causing the heart to assume a more transverse position on the diaphragm?

Dr. John P. Anderson, Cleveland, O.—One woman had a myxedema apparently dating back for 50 years and although she was taking thyroid extract regularly, her metabolism was still 33 per cent below normal. She had a marked secondary anemia and angina pectoris, but her heart border by x-ray was normal.

It is possible that the question of cardiac hypertrophy depends on the degree of myxedema.

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to have you bring out how plain the signs of myxedema are in these patients at the time they present themselves with cardiac involvement.

Dr. George Fahr, Minneapolis, Minn.—Before I answer the questions which have been asked of me, I want to make a general statement, namely that because the characteristic symptoms of myxedema are usually so striking, the symptoms of heart failure may become wholly submerged, and it is frequently only when the physician is looking for symptoms and signs of heart failure that he will pick them up in his myxedema cases. I will begin the discussion by answering Dr. Lerman. His statistics on the transverse diameter of the heart in myxedema just about agree with mine. I think 65 per cent of our hearts showed a dilatation in the transverse diam-

eter. If we go back to the physiology of heart muscle, to the work of Otto Frank done about 1896 and to that of Starling of about 1912, we see that the work performed by the heart is a function of the length of the heart muscle fibers. In other words, if you give a ventricle an increased amount of work to do, it can do it only when it dilates or when the muscle fibers lengthen. And as a corollary to this, when you make the heart muscle hypodynamic, in order for the hypodynamic heart to perform the same amount of mechanical work, the heart has to dilate or its muscle fibers must stretch before it is capable of performing this amount of mechanical work. This means that the very earliest sign of the hypodynamic condition of the heart muscle is dilatation. Therefore the moment you are sure that 60-65 per cent of your Massachusetts General Hospital cases of myxedema showed a definite dilatation, I think you have to agree that you have evidence of the onset of the condition of heart failure. Signs of congestive heart failure may not yet have shown up, but ultimately they are going to do so. In a study of the heart in hypertension I have seen it time and time again that the heart first dilates a little and may keep on dilating for a number of years before definite symptoms of congestive heart failure appear.

I think the next question, and a very pertinent one, was asked by Dr. Herrmann. It is one I should have taken up more fully in my paper, but in my hurry to get through I forgot about it. This concerns the amount of hemoglobin and the red cell count in these cases. As you know, when the red blood cell count drops, the viscosity of the blood drops with it and if the mean pressure stays approximately the same, the minute volume of the heart must increase proportionately to the decrease in viscosity. As Dr. Ronzoni and I showed many years ago, in cases of severe anemia the minute volume may increase more than 100 per cent and therefore with this lowering of the red count, we get a tremendous increase in the work of the heart. Moreover when the red count is lowered very far, it is possible that under reduced velocity of circulation a condition of mild anoxemia might result. In our cases of myxedema the red count varied between three and one-half million and four and one-half million. This decrease in the cell count would lead at the best to only a 10 to 25 per cent increase in work of the heart provided the mean blood pressure remained the same. Of course this does not mean a 10 to 25 per cent increase in the work of the normal heart, but it means a 10 to 25 per cent increase in the work of a myxedema heart. As you very well know, the minute volume in myxedema is very much reduced so that the work of the heart is also very much reduced in myxedema. In the study of our cases we have seen the dilatation of the heart go down to normal and symptoms of congestive heart failure recede at the same time that the red blood cell count remained practically the same as it was before we gave thyroid extract; so I do not think that secondary anemia is an important factor in the production of heart failure in myxedema. The other question of Dr. Herrmann relating to the proteins of the blood in myxedema was a very pertinent one. I have been investigating the proteins of the blood and the colloid osmotic pressure in relation to edema formation for a number of years, and I have some information on this factor in myxedema. One of our cases of myxedema heart also had a marked lowering of serum albumin and the osmotic pressure of the plasma colloids so that this was undoubtedly a factor in the formation of edema in her case. In her case, dilatation of the heart receded and passive congestion of the liver and dyspnea disappeared before the plasma proteins returned to normal. In one other case where I have investigated the lowering of the serum albumin, it has been very slight and in consequence the lowering of the osmotic pressure of the plasma colloids was undoubtedly very slight and therefore this could, at the best, be only a very slight factor in the production of edema. Moreover, the heart failure symptoms had disappeared before the plasma proteins were back completely to normal, showing that this factor is probably of very slight importance.

There was a question about "frank congestive heart failure" by Dr. Lerman. I cannot explain why he got only one case of frank congestive heart failure in thirty cases of myxedema, unless he is speaking of a very advanced degree.

One of those who entered into the discussion talked about minus basal rates, apparently as synonymous with myxedema. I want to emphasize very vigorously that a minus thirty basal rate doesn't necessarily mean myxedema or hypothyroidism. Anyone who has a large experience with a group of girls on a university campus who have high I.Q.'s, fast mental reaction time, and who often lead in their classes, will know that a certain percentage of them have a rate of minus thirty or thereabouts. There is no reason to believe that these are cases of either myxedema or hypothyroidism because they have not the symptoms of myxedema. I am inclined to believe, although I have no very good proof of it, that this minus rate has to do with some disturbance in the pituitary gland function. For me, the outstanding symptoms in myxedema are those of the central nervous system, and our studies have shown that the I.Q.'s go down very low and the reaction time slows up very decidedly. Also there is definite loss of memory in cases of myxedema. But in these young ladies with negative rates, these factors of central nervous disturbance are not present.

To two gentlemen who asked me about cases of myxedema heart with angina pectoris—I have seen only one case with angina pectoris. But in the literature you will find that there are many cases of myxedema with angina pectoris. In some of these cases the symptoms of angina pectoris disappear on thyroid treatment, but in others the angina pectoris increases on thyroid medication.

Dr. Pardee asked me a question about the myxedema symptoms. In those cases where we had the severest cases of heart failure, the myxedema symptoms were outstanding. They answered questions very slowly; their I.Q.'s as measured by our university psychologist were very low; their reaction time was tremendously slowed down; they had the characteristic puffy eyelids and the narrowed eye-slits. They had dry and scaly skin usually, rather than the thick and myxedematous type of skin. The symptoms were very marked in those cases with severe cardiac symptoms and a very marked dilatation of the heart. All of these cases had their myxedema for periods of time from anywhere from three to six or eight years. My youngest patient, a girl of nineteen, with a very moderate degree of heart failure, had had her symptoms of myxedema for a year or less. Only one of our cases had a definite thyroiditis with a hard woody gland. The young lady above mentioned had had some pain in her neck a year prior to the onset of symptoms. I couldn't say whether that was a thyroiditis or not.

In answer to Dr. Read concerning the correlation between dilatation of the heart and the electrocardiographic changes: if you mean do we always find the characteristic electrocardiographic changes when we find dilatation of the heart, then I would say yes. But if you have a patient who has been on thyroid extract for a long period and you then take him off the thyroid medication, you will find that the electrocardiographic changes sometimes come on a few months earlier than the marked dilatation and congestive heart failure symptoms. I mentioned that we had three cases of true myxedema in which we had no symptoms of a congestive heart failure and no dilatation of the heart; yet in all these cases the electrocardiogram shows a flat T. I haven't called these cases myxedema heart despite the fact that the electrocardiogram shows changes in the mechanism of the heart.

Discussion of paper by Drs. E. J. Kepler and A. R. Barnes. (See p. 102.)

Dr. George Fahr, Minneapolis, Minn.—Dr. Kepler, I want to be absolutely certain about this: Did you find that if you equated the heart weight to the body weight in all these cases of exophthalmic goiter or hyperthyroidism with adenoma the heart weight ratio was higher than the normal?

Dr. Wallace M. Yater, Washington, D. C.—In connection with the subject of hypertrophy, it is very interesting to note that the degree of hypertrophy in hyperthyroidism is slight when compared to that which occurs in hypertension. In hypertension the minute-volume output of the heart is not much changed, but the weight of the heart becomes greatly increased as a rule, whereas in hyperthyroidism the minute-volume output of the heart is greatly increased but the weight of the heart is relatively little changed. Apparently obstruction to blood flow is a much greater strain than increase in minute-volume output with lessened resistance to blood flow.

The question of malnutrition as a factor in the size of the heart is very important, as had been shown by a number of men in experimental work with animals. When the nutrition of animals maintained in a state of chronic hyperthyroidism is kept normal, the heart gains moderately in weight, sometimes as much as 50 per cent over the normal limit. If, however, malnutrition sets in, the weight that the heart has gained is rapidly lost, and when malnutrition is severe, a small, atrophic heart may result.

Dr. T. R. Harrison, Nashville, Tenn.—The relatively slight degree of cardiac hypertrophy in these cases is of great interest. Probably it is related to the fact that the work of the heart per beat is not much increased in patients with thyrotoxicosis. Other types of cardiac disorder are likely to be associated with increased work per beat as well as increased work per minute. It is likely that hypertrophy is dependent on the work per beat rather than on the work per minute.

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask Dr. Kepler how many cases of heart failure there were without auricular fibrillation being present and the approximate age of those patients.

Dr. E. J. Kepler, Rochester, Minn.—Regarding Dr. Fahr's question I may say that the weight of the heart was greater than the weight calculated from the standard in about one-half the cases, if the usual weight of the patient was used in making the calculation. If the last recorded weight of the patient, which closely approximates the actual weight of the body at the time of death, was used, it was found that in nearly every instance the weight of the heart exceeded the standard. Furthermore, we used as a standard the figures which Smith gave as the maximal normal weight of the human heart. In other words, we selected the most rigid standard available and found that in one-half the cases the weight of the heart exceeded the standard.

It is important to bear in mind, however, that, strictly speaking, we are discussing in this paper a disturbance in the ratio of heart weight to body weight; and we assume that if this ratio is increased, there has been a "morbid enlargement or overgrowth" of the heart, or, in other words, hypertrophy. At the present time we have no reason to believe that such an assumption is incorrect.

Dr. Pardee, I believe, raised the question of the frequency of auricular fibrillation with congestive heart failure. Practically all of the patients who had congestive heart failure had auricular fibrillation or auricular flutter.

The question also has been raised regarding the part which age plays in the production of congestive heart failure in hyperthyroidism. It is well recognized, clinically, that congestive heart failure in hyperthyroidism is a phenomenon encountered rarely in young patients and comparatively frequently in middle-aged and elderly patients. Consideration of our data does not, however, enable one to formulate an opinion regarding the influence which age has in the production of congestive failure because the cases are distributed unevenly through the various decades. The relationship of age to congestive heart failure can be studied best from clinical data. Our data do show, we believe, that congestive failure may occur in hyperthyroidism in the absence of any independent cardiac disease, and purely as the result of hyperthyroidism, plus the physiological diminution of cardiac reserve incidental to advancing years.

Discussion of paper of Drs. Morris W. Lev and Walter W. Hamburger. (See p. 109.)

Dr. George Fahr, Minneapolis, Minn.—I should like to ask Dr. Lev something about the diastolic pressures in these cases. I have always been surprised that we do not have more angina pectoris in severe exophthalmic goiter than we do. From determinations of minute-volume we know that in the cases described here the minute-volume will be at least double. The heart is not as efficient a machine against increased minute-volume as it is against pressure, so that when the minute-volume has doubled, the heart is requiring a consumption of oxygen more than double the normal.

Practically all the flow through the coronaries takes place during diastole. The diastolic time is cut down because these hearts are rapid. As we all know, the majority of cases of hyperthyroidism do show a lower diastolic pressure. If only a little coronary disease is present then, all you need to do is to lower your diastolic pressure a little bit and you can expect to have angina. It would be very interesting if we could find out in these cases of angina pectoris whether the diastolic blood pressure had been lowered, say down to 50 or some value like that, such as we once in a while find in the clinic.

Dr. Louis F. Bishop, Jr., New York, N. Y.—I should like to ask Dr. Lev what the electrocardiographic findings were in this series of cases of angina associated with hyperthyroidism. I should also like to ask if fibrillation was present in any of the cases with pain or whether there were any examples of paroxysmal tachycardia.

Dr. Morris W. Lev, Chicago, Ill.—In answer to Dr. Fahr, the diastolic pressures of all of our patients were normal or increased. We did not have any unusually low diastolic readings. If anything, they tended to be above the usual rate.

In answer to the question regarding the electrocardiographic pictures, in this particular series we took special pains to exclude those patients who might be accused of being frank coronary cases, or of having any other cardiac disturbance judging from the electrocardiographic pictures.

None of our patients, as I recall, had any auricular fibrillation or paroxysmal tachycardia. Anything that might have suggested that the patient was suffering from something other than angina would have excluded that case from our series.

Discussion of paper of Drs. Johnson McGuire and Margaret Foulger. (See p. 114.)

Dr. Harold E. B. Pardee, New York, N. Y.—Will Dr. McGuire explain what he means by "rolling contour of the T-wave"? Also did he obtain more than one lead of these dogs? If not, it is hard to see how the observations can be final, because the lack of variation in one lead is not an indication that the other leads are also unchanged.

Dr. Johnson McGuire, Cincinnati, O.—In regard to the definition of "rolling contour," I am very much interested to know if anyone can tell where that expression originated. It didn't with me. When I reviewed the literature, I found the expression rather often. To me it simply means that the summit of the wave is broad and not peaked. In normal young people with "T" waves of high voltage the wave rises sharply to a relatively sharp summit. In our examples the apex of the wave was smooth and sloping. I shall add a diagram to my paper to illustrate this difference.

In regard to the question about leads, I think nowhere have I found any description of changes occurring in thyrotoxicosis except in Lead 2, and in our dogs Lead 2 was used. I think it is an interesting suggestion that other leads should be examined, especially as in one or two of the cases which I showed, following the administration of thyroid extract, important changes occurred in Lead 1.

Discussion of paper of Dr. Lewis M. Hurxthal.

Dr. E. J. Kepler, Rochester, Minn.—What was the frequency with which demonstrable enlargement of the heart took place and was followed by a diminution in size?

Dr. Bayard Holmes, Chicago, Ill.—Has Dr. Hurxthal compared the effects of digitalis alone and Lugol's solution alone in regard to their ability to produce improvement of the cardiac dilatation before operation? My experience personally has been that digitalis alone has had comparatively little effect while Lugol's alone had the result that he has demonstrated here.

Dr. Lewis M. Hurxthal, Boston, Mass.—About the frequency of dilatation, there were eighty cases without congestive heart failure. Of those eighty, nineteen showed definite changes as shown by superimposition of films. Eight of those were larger, seven were unquestionably larger, and four were smaller. Of the cases which showed larger hearts after operation, there were one or two with postoperative myxedema. Some had definite hypertensive disease and in one or two we felt that it could readily be concluded that the increase or gain of weight had something to do with it. We had one boy with severe exophthalmic goiter who weighed ninety pounds before operation and one hundred and fifty pounds after operation. He had gained two-thirds of his body weight. Although the diaphragm was higher after operation in his case, nevertheless we felt that the heart shadow was definitely larger.

In all cases with congestive heart failure there was a definite reduction in the size of the heart. In twenty-five cases of auricular fibrillation, definite reduction in the size of the heart took place in fifteen. In other words, congestive failure, not auricular fibrillation, is probably the thing which causes the dilatation. We have been able to check cases of nonthyroid heart disorders with congestive heart failure and we have been able to demonstrate the same thing, but not so conclusively because there is usually fluid in the chest, making comparisons difficult.

About the use of digitalis and Lugol's solution, I do not believe any rule can be laid down. We have purposely withheld Lugol's solution in patients with auricular fibrillation and have given them digitalis and had excellent results; that is, a relief of congestive heart failure and a certain amount of slowing of the pulse. We have also withheld digitalis in some cases and given Lugol's and obtained good results. In other cases where Lugol's solution had been given and edema had increased, digitalis cleared all signs of congestive heart failure. Of course, knowing one will work in some cases and the other will work in other cases, we give them both together in this type of case as soon as the patient enters the hospital.

Discussion of paper of Drs. Paul S. Barker, Anne L. Bohning, and Frank N. Wilson. (See p. 121.)

Dr. G. Werley, El Paso, Tex.—I noticed, if I understood, that the mortality of operation in fibrillation cases was 20 per cent. I do not understand whether these cases were operated upon during the fibrillation or after the heart had been corrected by digitalis and iodine. I want to bring up our little experience in El Paso.

It seems to me that a much safer method of handling those cases would be to use x-ray and radium, because in our small series of cases we have had no mortality at all. The patients as a rule have not been put to bed. They have not been prepared in any way, and the results have been perfectly good. The treatment is prolonged, but I cannot see any difference between the end-results in these cases and in the cases that were operated.

Dr. George Fahr, Minneapolis, Minn.—I understood you to say, Dr. Barker, that there were signs of toxic effect before there was an increase in the work of the heart. That seems very strange to me, and I should like to ask how you measured the work of the heart.

Dr. Lewis M. Hurxthal, Boston, Mass.—I should like to discuss a few points which bear on the question of thyrotoxicosis damaging the heart. In the first place, dis-

turbances of conduction; i. e., various types of heart-block, are rare in hyperthyroidism. When present, they can usually be ascribed to other things. Another thing that we must not forget is that there is apparently a reversible change. After relief of hyperthyroidism, the heart muscle, from the functional standpoint, seems just as good as before the onset of hyperthyroidism, excluding the possibility of established fibrillation. It seems to me therefore that there is not much evidence of damage to the heart itself from thyroid toxicity.

Dr. E. J. Kepler, Rochester, Minn.—The mortality rate of hyperthyroidism associated with auricular fibrillation seems to be unduly high in the series of cases presented. It occurs to me that the energetic treatment of these patients with digitalis may be a factor in part responsible for this. I am of the opinion that digitalis should be used with caution in treating hyperthyroidism. At the present time digitalis in the treatment of congestive failure associated with hyperthyroidism is used comparatively rarely at the Mayo Clinic. Treatment with ammonium nitrate and salyrgan usually results in prompt diuresis and compensation is restored without the use of digitalis. When overtreatment with digitalis is used, undesirable toxic effects may appear before the pulse rate or cardiac decompensation is affected.

Dr. Lewis M. Hurxthal, Boston, Mass.—We are using digitalis routinely in all cases of auricular fibrillation except in cases of fibrillation without congestive heart failure, in which the rate does not average more than 100 per minute. The mortality at the Clinic up to 1928 on the 143 cases of thyrocardines with congestive heart failure or auricular fibrillation was only three per cent. The mortality since that time in the general run of cases is around one per cent. I think that is about the same percentage of mortality that is found in any thyroid clinic.

Personally, I have never seen any harmful effects from using digitalis in individuals with hyperthyroidism.

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask about the excretion rate of digitalis in these patients. It has seemed to me, although I have made no statistical study, that patients with hyperthyroidism need more digitalis than the ordinary patient. I have followed two patients whose metabolism was varying from time to time. As the metabolic rate would go up, the need for digitalis would increase.

I should also like to know in connection with this mortality rate if the patients who died were under what you would consider proper digitalis control at the time of operation or if they were culled from the days before proper digitalis control was understood.

Dr. Paul S. Barker, Ann Arbor, Mich.—I shall try to answer some of the questions. Several of our patients were given quinidine prior to operation and somewhat over half of them returned to normal rhythm, but in all of these the fibrillation returned.

I admit that the mortality in these cases seems high. You have no doubt noticed that the age of these patients with fibrillation is considerably above the average age of patients with toxic goiter. Many of them were in poor condition and were not operated upon for this reason. The mortality was very high in this group. An effort was then made to see what could be done by means of thyroidectomy in similar cases. It is my belief that the results are better with thyroidectomy than without it, excepting in the very aged and those in extremely critical condition. Since the time at which these cases were treated, of course our ability to treat such cases has improved, and our mortality is much lower now, partly because of improved management in the postoperative period.

Regarding the work of the heart in the two cases that I cited, between attacks they were apparently perfectly normal people, with normal heart rate and normal blood pressure, and this is evidence that the work of the heart was not increased.

They did not have arteriosclerosis. The work of the heart, however, was not actually determined in these patients. I have estimated the work of the heart in other patients, and also in the cases of Davies, Meakins, and Sands,* in which the necessary data were given in connection with studies of the blood flow. The work of the heart was estimated according to the method described by Dr. Fahr,** and it is increased in fully developed Graves' disease.

We have not seen harmful effects from digitalis. We have seen beneficial effects in some patients. In others, however, we have given full doses without any beneficial effects that we could determine. I do not know why digitalis is less effective in hyperthyroidism unless perhaps it is utilized, eliminated, or destroyed more rapidly, or because vagus tone is low. It is well known that patients with toxic goiter require much larger doses of morphine and also that they tolerate larger doses of quinine than the average patient, and no doubt experience will show that they tolerate other drugs in larger amounts.

It is my impression, although I do not have the figures, that the rate of excretion of digitalis is increased in hyperthyroidism. The manner of administering digitalis in this group of cases was such that we had to take into account not only the tolerance to a single large dose, but also the excretion rate, and it seems that both are increased in these patients.

Discussion of paper of Dr. John P. Anderson. (See p. 128.)

Dr. William D. Reid, Boston, Mass.—What was the maximum and average amount of quinidino given to these patients?

Dr. John P. Anderson, Cleveland, O.—I am sorry that I did not prepare any statistical record of the amount used. I would say that the average patient received about six doses or a total of thirty grains. Sometimes one or two doses prove sufficient, but it is not at all infrequent for patients to require the second and third day's course of quinidine therapy and a few required the full four days' course. One such patient still had an abnormal rhythm on the fourth day, and I ordered the quinidine to be stopped at midnight. A normal rhythm was established about two o'clock that morning.

Discussion of paper of Drs. Morris W. Lev and Walter W. Hamburger. (See p. 134.)

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask whether the patients were at rest before the control electrocardiogram was taken.

Dr. Morris W. Lev, Chicago, Ill.—The taking of electrocardiograms was no novelty to them. They had had electrocardiograms taken previously for routine work, and there was no mental effect or any particular excitement. As a matter of fact, they were at rest at least fifteen minutes before anything was done.

*Davies, H. W., Meakins, J., and Sands, J.: *Heart* 11: 299, 1924.

**Fahr, George: *Proc. Soc. Exper. Biol. & Med.* 24: 405, 1927.

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A CLINICAL TYPE OF PAROXYSMAL TACHYCARDIA OF VENTRICULAR ORIGIN IN WHICH PAROXYSMS ARE INDUCED BY EXERTION*

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INTRODUCTION

PATIENTS who are subject to simple paroxysmal tachycardia, paroxysmal flutter, or paroxysmal auricular fibrillation not infrequently describe individual attacks that were precipitated by exertion or excitement. Ordinarily the attacks are separated by comparatively long intervals of time and cannot be induced at will. Rest has little or no effect upon the duration of the abnormal rhythm.

It is our purpose to call attention to a type of paroxysmal tachycardia of ventricular origin in which moderate exertion invariably or almost invariably brings on an attack. While long attacks lasting several hours or days sometimes occur, a rapid succession of short paroxysms is more usual. In the pauses between these short attacks ventricular extrasystoles occur singly or in salvos of two to five or more. Rest is often followed by a gradual decrease in the length and frequency of the paroxysms and the return of normal rhythm. From a clinical standpoint this condition is quite different from paroxysmal tachycardia of the ordinary type. It may be easily overlooked. Many of the patients subject to it show no signs of structural heart disease and no disturbance of the cardiac mechanism while at rest. A complaint of palpitation on exertion or the discovery of an extrasystolic arrhythmia arouses no suspicion that a serious cardiac disorder is present, and it is only when the patient is examined after exertion that the real nature of the disorder is discovered.

In France there has been a tendency, particularly evident in the writings of Gallavardin and his associates,^{1, 2, 3, 4, 5} to divide paroxysmal tachycardia into a number of clinical types, which may or may not differ fundamentally. According to Gallavardin^{4, 5} attacks of paroxysmal

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tachycardia of the classical type (*Tachycardie paroxystique type Bouveret*) are not as a rule preceded or followed by extrasystolic arrhythmia. When isolated extrasystoles do occur in association with the onset or termination of the paroxysms, they are not of the same electrocardiographic type as the beats that constitute the rapid rhythm, and this rhythm is not regarded by Gallavardin as necessarily due to a succession of extrasystoles. In this type of paroxysmal tachycardia the attacks are, as a rule, relatively long and rather infrequent. Gallavardin has, however, described a group of cases of paroxysmal tachycardia of supra-ventricular origin in which the attacks were extremely frequent and were easily provoked by exertion and excitement.³ In these cases false arrest often occurred; i. e., the rapid rhythm was frequently interrupted by short periods of normal mechanism. Gallavardin² apparently regards cases of this kind as a distinct variety of paroxysmal tachycardia of the classical type in which the paroxysmal center is unusually excitable; he refers to them as examples of "*Tachycardie paroxystique à centre excitable*."

He considers paroxysmal tachycardia in which the attacks are preceded or followed by isolated extrasystoles of the same electrocardiographic type as the beats which constitute the ectopic rhythm as belonging to an entirely different group;^{4, 5} "*L'extra-systolic à paroxysmes tachycardiques*." In the majority of the cases of this group the abnormal rhythm consists in a succession of short paroxysms lasting from a few seconds to one or two minutes (*tachycardie en salves*) separated by periods in which beats of normal origin are interspersed with extrasystoles occurring singly, in pairs, or in short runs. In rare cases the paroxysms are very long, and Gallavardin⁴ has reported an instance in which the abnormal rhythm persisted continuously for a period of thirty days. At the beginning and toward the end of this period, however, the tachycardia was occasionally interrupted by the occurrence of beats of normal origin.

It will be seen that the cases described in this article correspond, on the one hand, to the cases referred to by Gallavardin as *tachycardie en salves*, and, on the other, to the group which he designates *tachycardie paroxystique à centre excitable*.

ILLUSTRATIVE CASES

CASE 1.—An American farmer, aged thirty-one years, was admitted to the University Hospital, August 29, 1924, complaining of breathlessness, and attacks of rapid heart action.

Present Illness.—He had always been well and had had an unusual capacity for work until December 29, 1917. On that date while he was chopping wood, his heart suddenly began to beat with extreme rapidity and violence. He felt a "buzzing" in his chest, and was soon covered with cold perspiration. He was very weak and lay down on a log, but, after a few minutes, got up and managed to reach his home, a half mile away. On entering the house he sat down on a couch and suddenly became unconscious, remaining so for "about one hour." When he regained consciousness, the heart action was normal. A second attack occurred one week later, when he

learned through a neighbor that his physician thought that he would not live long. He remained in bed for six weeks and was then taken to a hospital for a fortnight. While in the hospital he was given spartein, and he continued this drug for about one year after returning home. During this time he was frequently short of breath, but he had no more attacks until December, 1918, when a paroxysm came on while he was hunting rabbits in deep snow. He could not walk home, but had to be brought to the house with a horse and wagon. The rapid heart action continued for three or four hours. From that time the attacks were so frequent that he was almost completely incapacitated by them. They were usually brought on by exertion, eating, or excitement. They varied in duration from a few seconds to seven days. He took many kinds of drugs, including spartein, which had previously seemed to give him relief, without effect. On several occasions he became unconscious for a brief interval, and he believed that each time the fainting spell occurred just after the paroxysm came to an end. The cessation of the rapid heart action was often followed by nausea and vomiting.

Past History.—He had had a severe attack of scarlet fever without complications at thirteen years, a severe attack of pneumonia at seventeen, and a light attack of influenza in 1918. Several years before his illness he had a perirectal abscess which healed after drainage. He gave no history of rheumatic fever, chorea, or tonsillitis and denied having had venereal disease. The marital and family history were not significant.

On examination, the patient was well developed, and well nourished. There was no cyanosis and no objective dyspnea; no congestion of the neck veins, or throbbing of the peripheral arteries. The radial and brachial arteries were slightly thickened but not tortuous or beaded. There was no tracheal tug, substernal dullness, or pulsation in the suprasternal notch. There was no heaving of the precordia. The left border of the heart could not be definitely located by inspection or palpation, but the left border of cardiac dullness was about two centimeters outside the nipple line. At the apex, the heart sounds were rather distant. At the base, the aortic second sound was slightly accentuated. There were no murmurs. The rhythm was disturbed by frequent extrasystoles, and bigeminy was present for brief periods. The examination of the abdomen and the extremities was entirely negative.

Laboratory Tests.—An x-ray examination of the chest showed nothing abnormal in the lung fields. The size of the heart was difficult to make out because of the presence of scoliosis, but the teleroeculogenogram showed a Danzer ratio of 0.49. The examination of the urine and of the blood showed no abnormalities. The systolic blood pressure was 130 mm. Hg, and the diastolic 69 mm. Hg. The Wassermann test was negative.

Special Studies.—An electrocardiogram taken on September 2 showed pronounced V-shaped inversion of the T-deflections in Leads II and III and bigeminy due to ventricular extrasystoles. The form of the extrasystolic complexes was exceedingly variable. An electrocardiogram taken on September 4 (Fig. 1) was similar in all respects except that no extrasystoles were present. Exertion (running up and down stairs) induced bigeminy and multiple extrasystoles, as many as six in succession; the form of the extrasystolic complex was again variable. As a rule no two extrasystoles of a succession were alike in form or spacing. After the exercise had been repeated several times, however, a long attack of paroxysmal ventricular tachycardia was precipitated. The paroxysmal rate was about 200 per minute and the rhythm slightly irregular. The inhalation of amyl nitrite had no effect upon the cardiac mechanism. Three grains of quinidine were given and the attack stopped suddenly about twenty-five minutes later. In the later stages of the attack the rate varied; it rose as high as 243 per minute and fell as low as 165 per minute.

On September 5 an attack came on spontaneously while the patient was using a bed pan. It stopped after fifteen or twenty minutes. Vagus pressure was without

effect. On this date attacks could be induced at will by exertion. The paroxysmal rate varied from 171 to 231. Two paroxysms separated by a single normal beat differed in rate by 32 beats per minute (Fig. 2). The rhythm was sometimes conspicuously irregular (Fig. 2) during the paroxysms; at other times the irregularity was very slight (Fig. 1). From September 6 to 10 the patient was given quinidine sulphate; 0.4 gm. at 8:30 A.M.; 0.2 gm. at 11:30 A.M. and at 3:30 P.M. During this period he was free of attacks not only while in bed but also while he was walking about. He asserted that he had not felt so well in months. Attacks could still be induced by exertion, and extrasystoles were frequently present. Quinidine was dis-

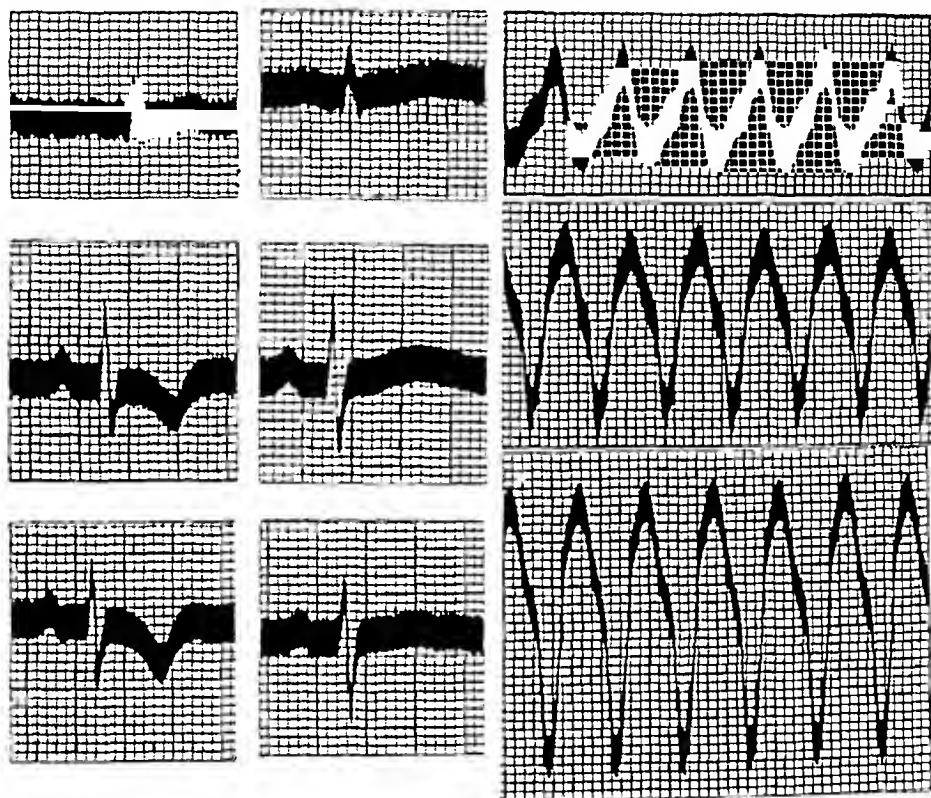


Fig. 1.—Case 1. Left-hand column: Leads I, II and III in order. Taken on September 4, 1924. The T-deflections are sharply inverted in Leads II and III.

Center column: Leads I, II and III in order. Taken on September 8, 1924, when the patient was receiving 12 grains of quinidine sulphate per day. The T-deflections are now upright.

Right-hand column: Leads I, II and III in order. Taken on September 5, 1924, during a long attack of ventricular tachycardia. Heart rate 212 per minute. There is no definite arrhythmia. (In all tracings a deflection of 1 cm. represents a potential difference of 1 millivolt.)

continued on September 9, but no paroxysms occurred until September 12. On this date the electrocardiogram showed frequent auricular extrasystoles as well as ventricular extrasystoles. Eight to ten auricular extrasystoles sometimes occurred in succession (Fig. 3). The patient had several attacks of paroxysmal ventricular tachycardia, and these were frequently interrupted by runs of auricular extrasystoles (short attacks of paroxysmal auricular tachycardia) which occurred at a slightly more rapid rate than the beats of the ventricular paroxysm and therefore temporarily suppressed the ventricular pacemaker (Fig. 3). When the rates of the paroxysmal auricular center and of the paroxysmal ventricular center were nearly the same, interference took place, and the ventricular complexes were transitional in form between the complexes of the paroxysmal auricular and those of the paroxysmal ventricular series (Fig. 3).

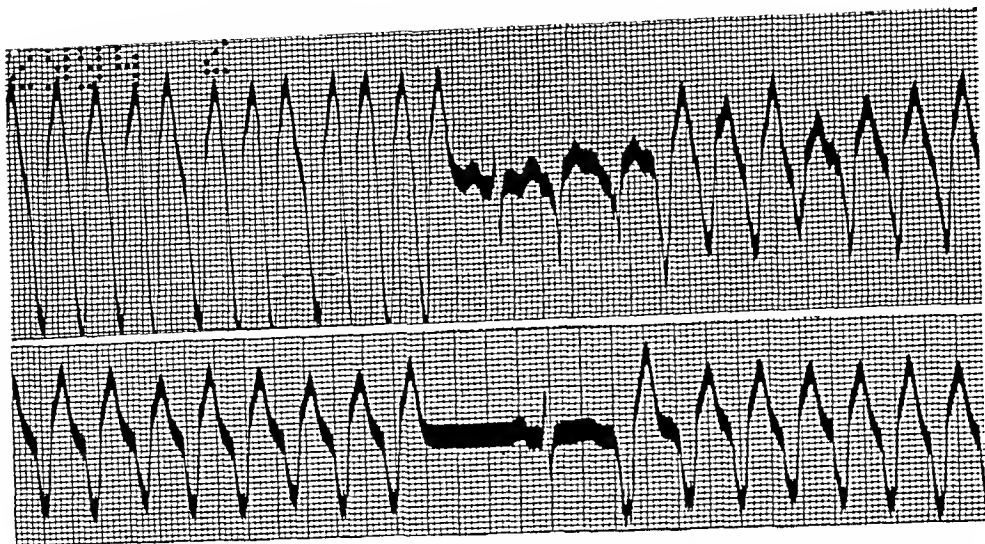


Fig. 2.—Case 1. Upper curve: Lead III showing the end of one attack of ventricular tachycardia and the onset of another (September 5, 1924). The rhythm was definitely irregular during the paroxysms. During the first paroxysm the rate was approximately 220 per minute; during the second, approximately 188 per minute.

Lower curve: Lead III, taken September 12, 1924. Two paroxysms of ventricular tachycardia are separated by a single beat of sinus origin. During the first paroxysm the heart rate was approximately 178 per minute; during the second, approximately 183 per minute. The interval which separates the last beat of the first paroxysm from the first beat of the second (1.48 second) is not an exact multiple of the paroxysmal cycle length which averages 0.337 second for the first paroxysm and 0.328 second for the second.

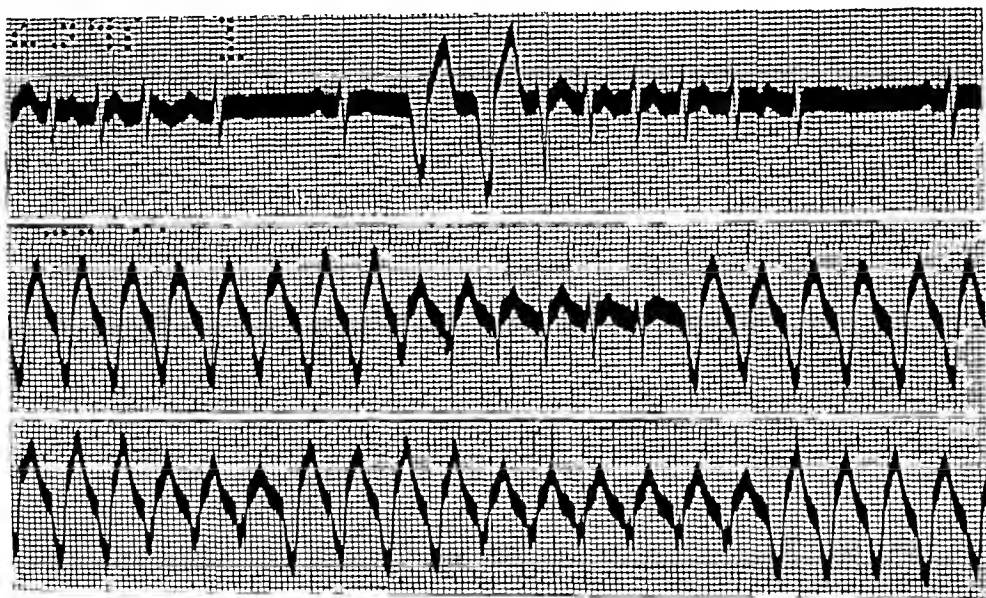


Fig. 3.—Case 1. All tracings taken September 12, 1924. Lead III only. Top tracing: Short runs of auricular extrasystoles, usually preceded by one or two ventricular extrasystoles.

Middle tracing: An attack of ventricular tachycardia temporarily interrupted by a short run of auricular extrasystoles occurring at a slightly more rapid rate than the beats of ventricular origin (the rate was approximately 185 per minute in both cases). At the onset of the auricular paroxysm complexes of transitional form due to interference are seen. Measurements of the length of a number of periods of interruption of this type indicate that the auricular impulses often reached the ventricular center and brought the ventricular paroxysm temporarily to an end.

Lower tracing: Two short runs of complexes of transitional form temporarily interrupting a ventricular paroxysm. These transitional complexes are due to interference between the ventricular center and an auricular center producing paroxysms of stimuli at approximately the same rate. An auricular complex is superimposed upon the T-wave of each of these transitional complexes except the last of each group.

The administration of quinidine was resumed on September 13 and continued during the remainder of the patient's stay in the hospital. One attack lasting thirty minutes occurred on this date and a few short attacks on the following day, but he was comfortable thereafter. Exertion failed to produce a long attack on September 13 and again on September 18, although many short attacks consisting of five or six beats in succession did occur (Fig. 4). Atropin (one twenty-fifth of a grain intravenously) on September 13 had no definite effect upon the frequency of the abnormal beats. The inverted T-deflections present on admission gave place to broad upright waves when quinidine was given (Fig. 1) and returned when this drug was omitted.

The patient was discharged on September 24. We have since learned that he was able to return to work but died suddenly while eating lunch a few months after he left the hospital. No further details could be obtained.

CASE 2.—An American plumber, aged fifty-two years, was admitted to the hospital October 24, 1929, complaining of shortness of breath and palpitation.

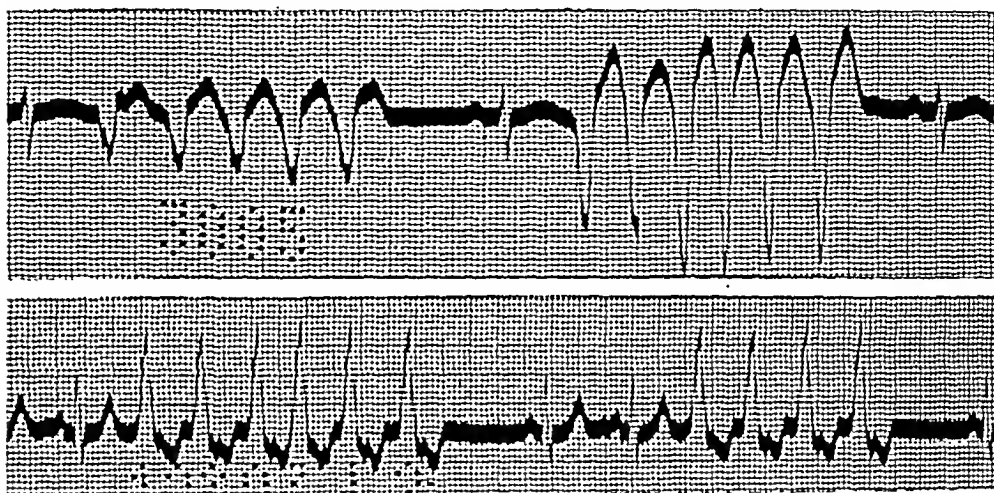


Fig. 4.—Upper tracing: Case 1, Lead III. Taken on September 18, 1924. At this time the patient was receiving 9 to 12 grains of quinidine sulphate per day. Exertion precipitated only short runs of ventricular extrasystoles; no long attacks.

Lower tracing: Case 4, Lead II. Short paroxysms of ventricular tachycardia occurring in rapid succession. The auricles responded to the ventricles during the paroxysms.

Present Illness.—He was entirely well until August, 1927, when he had an attack of palpitation after eating which lasted one or two hours and produced slight dizziness. A second attack occurred two weeks later and four or five other attacks during the remainder of the year. At the onset of these later attacks he noticed a choking sensation and a feeling of pressure in the region of the ensiform. During the attacks he felt faint; he had a beating sensation between the eyes and a "wooden" feeling in the head. He would forget things that he had heard only a few minutes before.

In January, 1928, he became short of breath and had to give up work. Sweeping or any other slight exertion would bring on an attack which might last eight to ten hours. He had to lie down most of the time because of giddiness and faintness. Occasionally he had sharp shooting pains in the precordia with dull pain in the left shoulder, but without radiation to the arm. These pains were not relieved by nitroglycerin.

In June, 1928, he was at his worst; slight exertion such as walking up a few steps would precipitate an attack. He had frequent fainting spells and often felt as though he were going to die. During an attack he could hardly feel his heart beating. In January, 1929, he began to improve and had since felt much better, but still had

frequent attacks and was unable to work. He had gained about ten pounds in weight. He had never suffered from orthopnea or cough. He had had no edema of the ankles.

The *past history* threw no light upon the etiology of the cardiac disorder. He had had the usual diseases of childhood but no scarlet fever, chorea or rheumatic fever. He denied venereal disease and had seven children living and well.

Physical Examination.—The patient was well developed and slightly obese. His complexion was ruddy and he did not appear ill. The skin, head, ears, eyes, and nose showed nothing abnormal. The teeth were artificial. The tonsils were slightly enlarged. There was no thyroid enlargement. The lungs were normal. The cardiac apex was felt in the fourth intercostal space 9 cm. from the midline. The area of cardiac dullness was not increased. There were no murmurs. The blood pressure was 150/90 mm. Hg. The abdomen and the extremities were negative.

Laboratory Tests.—On x-ray examination the heart was thought to be slightly

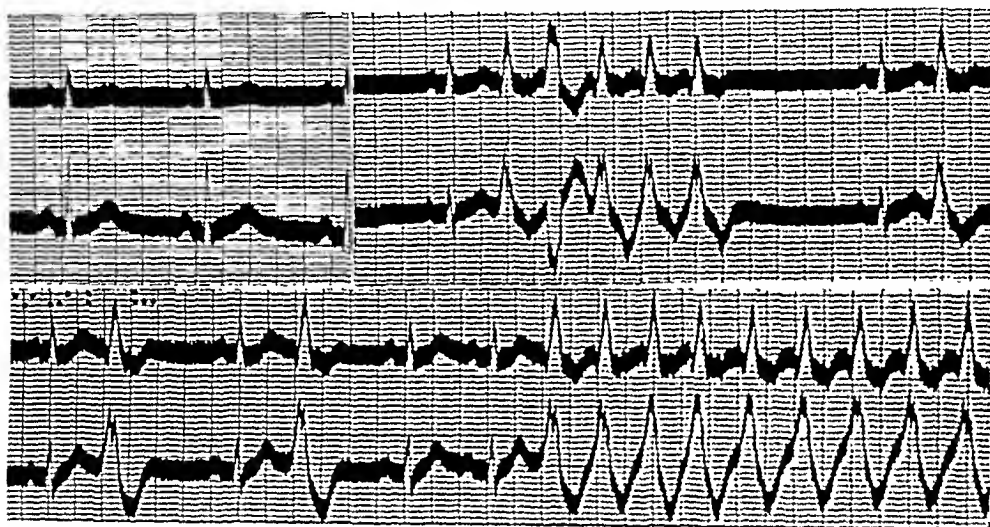


Fig. 5.—Case 2. Time in fifths of a second. Two leads taken simultaneously. Upper left curve: Leads I and II before exercise (October 28, 1929). Normal electrocardiogram.

Upper right curve: Leads I and III after exercise (November 6, 1929). A short paroxysm of ventricular extrasystoles arising at one center interrupted by a single ventricular extrasystole arising at a second center. During the paroxysm the auricles responded to the ventricles.

Lower curve: Leads I and III after exercise (October 28, 1929). A period of extrasystolic bigeminy followed by a paroxysm of ventricular tachycardia. Measurements of curves of this type indicate that in general the interval between two successive extrasystoles was not an exact multiple of the paroxysmal cycle length. Unfortunately, the ventricular rhythm was often somewhat irregular so that too much stress should not be laid upon this point.

enlarged to the right and the aorta appeared to be somewhat tortuous and slightly dilated. The Wassermann test was negative. The blood and urine were normal. The basal metabolic rate was 17 per cent below normal on two occasions.

Special Studies.—An electrocardiogram taken on October 14 was normal in every respect; the heart rate was 60 per minute. On October 18 the patient complained of pain in the precordia and irregular heart action. In the electrocardiogram every second normal complex, at times every normal complex, was followed either by a single extrasystole or by a series of from two to five, usually four, occurring in rapid succession. All of the extrasystoles were represented by complexes of the same type. The irregularity persisted for two or three hours.

At 9:40 A.M. on October 21 the electrocardiogram was normal and the heart rate was 69 per minute. Mild exertion (walking rapidly up and down a flight of stairs) sufficient to raise the sinus rate to 125 per minute was followed by a series

of short attacks of paroxysmal ventricular tachycardia separated by brief periods of bigeminy or trigeminy. The paroxysmal rate varied in different attacks from 166 to 184 per minute. When the patient rested, the disturbance gradually subsided, but returned on further exertion. It was observed that the paroxysms did not as a rule begin during the exercise but one or two minutes after it had been completed. Attacks were also induced by exertion on October 22.

On October 23 the patient was given a single dose of quinidine sulphate (0.8 gm.) at 1 P.M. At 2:35 P.M. the electrocardiogram was normal and the heart rate 73 per minute. The T-deflections were slightly flatter and broader than on previous occasions (quinidine effect). Paroxysms were induced by exertion several times during the afternoon; it seemed slightly more difficult to precipitate them than it had been previously. The paroxysmal rate varied from 168 to 188 per minute. No relation could be discovered between the paroxysmal rate and the sinus rate just before or just after the paroxysm.

From October 24 to November 1 the patient was given 0.4 gm. of quinidine sulphate three times per day. During this period he was comfortable and had no spontaneous attacks. At 3 P.M. on October 28 the electrocardiogram was normal (Fig. 5) and the heart rate 60 per minute. Exertion raised the sinus rate to 100 per minute and again produced paroxysms similar to those previously described (Fig. 5). Exertion also produced paroxysms on October 31; abnormal heart action persisted for eight minutes. Euphyllin 0.1 gm., three times per day, was substituted for quinidine on the morning of November 1. On the following morning walking up and down three flights of stairs four times (an amount of exertion not greater than that previously employed to induce attacks) was followed by a succession of paroxysms which began about one minute after the completion of the exercise and continued for five and one-half hours. Amyl nitrite had no effect. As many as 43 extrasystoles in succession were counted. While taking euphyllin the patient had frequent spontaneous attacks and also complained of nausea. When this drug was replaced by quinidine, he was again comfortable and practically free of extrasystoles so long as he remained quiet.

The patient was discharged on November 18, 1929. A recent letter (April, 1932) from his home physician (Dr. D. Pierpont of Ironwood, Michigan) states that he is feeling much better than when he left the hospital and can walk a mile without much discomfort, but is not able to work. His pulse rate is usually between 60 and 65 per minute. He has substernal pain at times especially on climbing stairs. A letter from the patient (April, 1932) states that he has not had a heart attack for about six months. He has substernal pain on exertion, but if he continues the exertion the pain subsides.

CASE 3.—We have had the opportunity of making less complete observations on a third example of this disorder. The patient was a woman in the late thirties. She had had typhoid fever but no other serious illnesses. There was no history of chorea or rheumatic fever. For several years she had noticed pronounced palpitation induced by exertion or excitement. There were no other symptoms except a rather marked feeling of exhaustion which varied greatly in intensity. The examination of the heart revealed no signs of structural disease. The thyroid gland was slightly enlarged but there were no symptoms or signs of thyroid intoxication. The remainder of the examination was negative. The electrocardiogram was normal when the patient was resting. Immediately after exertion each normal beat was followed by a succession of four to ten ventricular extrasystoles. In the course of a few minutes the extrasystolic salvos became less frequent, the number of extrasystoles in each group decreased and normal rhythm was established. The amount of exertion necessary to precipitate the disordered heart action was very small, and the patient found it practically impossible to do any type of work involving physical effort or

excitement. Quinidine sulphate (0.2 gm. two or three times a day) lessened the frequency of the attacks but did not abolish them.

CASE 4.—A fourth patient (male, aged twenty-five years) whom we have seen only once, displayed a similar disturbance of the cardiac mechanism, but in this instance there was no definite relation between exertion or excitement and the attacks. He complained of an increased tendency to fatigue during the preceding three years and of palpitation. The past history was negative. The examination revealed nothing abnormal except slight scoliosis, very mild anemia, and cardiac arrhythmia. There were no signs of structural heart disease. In the electrocardiogram every second normal beat was followed by a series of from two to seven ventricular extrasystoles (Fig. 4). Each ectopic impulse, except perhaps the first of each series, was conducted to the auricles. This is indicated not only by the notch on the downstroke of the inverted T-waves but also by the uniform length of the post paroxysmal pause (Fig. 4). There was no change in the cardiac mechanism during the few hours that the patient was under observation.

SIMILAR CASES DESCRIBED IN THE LITERATURE

We have not made an exhaustive study of the literature, but in a brief survey of the publications of recent years relating to paroxysmal tachycardia we have found a number of case histories similar to those given above.

The patient studied by Scott⁶ was a woman, aged thirty-nine years, who gave a history of typhoid fever and of vague rheumatic symptoms at twenty-two years of age. She had suffered from palpitation for about ten years. At first the attacks were not frequent or severe, and they gave her no particular concern. For the past year, however, she had been unable to work. Attacks of rapid heart action were easily precipitated by exertion and lasted from one to forty-eight hours. There was no evidence of structural heart disease, the blood pressure was normal, and the Wassermann test negative. Mild cardiac failure occurred in the longer attacks. The electrocardiograms were similar in all respects to those obtained in our cases. The abnormal beats arose in the ventricles and were conducted to the auricles. The effect of drugs was very carefully investigated. Nitroglycerin had no effect. Both atropine (0.02 to 0.03 grain) and adrenalin (10 to 15 minims of a 1:1000 solution intramuscularly) precipitated attacks. Long attacks could invariably be brought to an end by a single dose of quinidine sulphate (0.4 gm.). When quinidine was given regularly (0.2 gm. three times per day), the patient was free of attacks and was able to return to work. When the drug was discontinued some six months later the attacks returned, but they stopped again when the administration of the drug was resumed. We are informed (May, 1932) by Dr. Scott that this patient has recovered completely. She no longer takes quinidine and has had no attacks for several years. Examination of the heart shows nothing abnormal.

Two cases are briefly described by Wenckebach and Winterberg⁷ in their book on irregular heart action. The first patient was a woman forty-four years of age, who complained of severe palpitation on exertion. When she was at rest the cardiac rhythm was sometimes normal, sometimes disturbed by ventricular extrasystoles occurring singly or in groups of two to three. Mild exertion increased the frequency of the abnormal beats. More violent exertion was followed by short attacks of paroxysmal ventricular tachycardia. On one occasion the cardiac rhythm was normal and the heart rate 60 per minute. Exertion induced an attack which lasted for twelve minutes. At the onset the paroxysmal rate was 230 per minute, but in two minutes it had fallen to 183 where it remained until the paroxysm ended. The end

of this attack was followed by salvos of extrasystoles, and normal rhythm was only gradually reestablished.

The second patient was a woman, aged fifty-three years, who had always been well except for rheumatic fever twenty-eight years before. Three years before she began to have palpitation on exertion, and the amount of exertion necessary to induce this symptom had gradually diminished. When the patient was resting the cardiac mechanism was normal and the heart rate was 60 per minute. Exertion invariably induced attacks of ventricular paroxysmal tachycardia, and spontaneous attacks were also observed. After mild exertion the tachycardia began at once, but after more violent exertion there was a delay of one or two minutes. Electrocardiograms showed that this delay was due to the very rapid sinus rate. When the sinus rate was driven above the usual paroxysmal rate, the abnormal heart action did not begin until the sinus rate had fallen to the paroxysmal level. When this point was reached, interference between the two rhythms with ventricular complexes of transitional form occurred at the onset of the abnormal rhythm.

Anderson's⁸ patient was a boy aged seventeen years who complained of frequent attacks of palpitation during the previous three years. Attacks were induced by excitement and exertion but also occurred spontaneously. There was no history of rheumatic fever, chorea, scarlet fever, or diphtheria, and there were no signs of structural heart disease. At first the abnormal cardiac mechanism consisted in a rapid succession of short runs of ventricular extrasystoles, but later long attacks occurred. When taking quinidine (5 grains morning and evening) the patient was completely free of attacks. The discontinuance of this drug was followed by a period during which attacks could be induced by exertion, although the isolated extrasystoles that were usually numerous just before and just after an attack were entirely absent. At the beginning of one attack studied the auricles beat independently, but later the auricular rate was exactly one-half the ventricular.

Cases 4 and 5 of the series of cases of paroxysmal tachycardia reported by Gilchrist⁹ also belong to the group under consideration. The first of these patients was a man aged forty-one years who complained of short attacks of palpitation brought on by exertion. The heart was slightly enlarged to the left, but there were no other signs of structural heart disease. Aside from a secondary anemia the remainder of the clinical examination was negative. The patient was in the habit of smoking large quantities of strong tobacco.

When normal rhythm was present, the electrocardiogram showed very large inverted T-waves (Lead III), similar to those which occurred in our Case I. An electrocardiogram taken during an attack showed a very irregular succession of strikingly abnormal ventricular complexes. No auricular waves were visible. Alternation in the form of the ventricular complexes is seen at the beginning of one of the small strips of record reproduced.

The second patient, a man aged nineteen years, had suffered from attacks of giddiness and weakness for the past eighteen months. These attacks were precipitated by exertion. At first they lasted only four or five minutes, but more recently attacks lasting two or three hours had occurred. An electrocardiogram taken during an attack showed "an intimate mixing of short ventricular paroxysms, multiple and isolated extrasystoles, and occasional beats of normal origin." There was no evidence of structural heart disease. Attacks were easily induced by exertion. When taking seven grains of quinidine per day the patient was free of attacks and able to work. Vagal stimulation and large doses of digitalis had no effect upon the abnormal cardiac mechanism. In one of the tracings published the paroxysmal rhythm is nearly regular; a second tracing shows a very high grade irregularity.

The patient studied by Allan¹⁰ was a man aged fifty-three years who complained of short attacks of giddiness and faintness which had occurred off and on for the past

twelve years. Recently these attacks had become more frequent; the patient was convinced that exertion and excitement precipitated them. In some attacks he became unconscious, and typical Stokes-Adams seizures were observed while he was in the hospital. Between attacks the examination of the heart was entirely negative and the electrocardiogram was normal. Electrocardiograms taken during attacks showed runs of ventricular extrasystoles varying in duration from six to twenty-three seconds. Extrasystoles of the same type as those of the paroxysmal series occurred singly or in pairs between the periods of rapid rhythm. After the first few beats of the ectopic rhythm the auricles responded to every second ventricular contraction. Quinidine sulphate (0.2 gm. one to three times a day) completely abolished the attacks.

Hume¹¹ reported six cases of paroxysmal tachycardia occurring in soldiers in France. In four of these cases attacks were induced by exertion. They could not be induced by the administration of atropine (one-thirtieth grain) or adrenalin (two and one-half minims of a 1:1000 solution intravenously). None of the patients showed any evidence of structural heart disease. It was impossible to be certain that the attacks were ventricular in origin.

Willius¹² reported a series of five cases of paroxysmal ventricular tachycardia. He states that the attacks were related to exertion and excitement but gives no details.

COMMENTS

The most notable features of the group of cases under consideration are: (a) the relation of the attacks to exertion and excitement; (b) the absence in the majority of the cases of signs of structural heart disease; (c) the occurrence of many short attacks in rapid succession separated by periods of high grade extrasystolic arrhythmia; and (d) the effectiveness of quinidine in controlling the abnormal mechanism.

Because of the relation of the paroxysms to effort and emotion the attacks are exceedingly frequent and the patient is usually seriously handicapped. As a rule the disability is greater than that produced by a well-compensated valve lesion or by continuous auricular fibrillation without congestive failure. In those cases that have been followed for a considerable period of time there has been with one exception (Scott's case) little tendency to recovery. The frequent occurrence of ventricular paroxysmal tachycardia in coronary thrombosis and the relation of the pain of angina pectoris to effort and excitement suggest the possibility that coronary disease may be the cause of this disorder. There is, however, little evidence to support this view. It is not in harmony either with the youth of some of the patients or with the absence of clear evidence of structural heart disease in the majority. Typical anginal pain did not occur in any of the cases reviewed. In the case histories evidence of general arteriosclerosis, arterial hypertension, diabetes, and luetic infection, all of which are relatively common in cases of coronary disease, is conspicuously absent. It may be pointed out, however, that in one of our cases and in one of those reported by Gilchrist the T-deflections of the electrocardiogram were strikingly inverted in Leads II and III when the cardiac mechanism was normal. T-deflections of this type appear to be relatively frequent in cases of ventricular paroxysmal tachycardia

and are somewhat similar to the T-wave changes that are seen in coronary thrombosis. They evidently indicate a local change in the duration of the excited state in the ventricular muscle. Such a change may depend either upon a structural lesion or merely upon altered function dependent perhaps upon influences exerted by the vegetative nervous system. It is noteworthy that quinidine may profoundly alter the form of these inverted T-deflections (Case 1).

The relation of the attacks to exertion and excitement, the absence of signs of structural heart disease, and the fact that paroxysms are precipitated in some of the cases by adrenalin and atropine suggests that the cause of the disorder may lie in the vegetative nervous system rather than in the heart. Attacks appear to be induced in susceptible individuals chiefly by procedures that increase accelerator or diminish vagal tone. It is worthy of note, however, that none of the patients studied displayed any evidence of thyrotoxicosis. The abnormal mechanism is not very unlike that which Levy¹³ produced in animals under light chloroform anesthesia by the injection of adrenalin, nicotine, atropine, and other drugs and by direct or reflex sympathetic stimulation. Levy found that after removal of the adrenal glands and the sympathetic nerve supply to the heart these disturbances of the heart beat could no longer be induced by sympathetic stimulation; the injection of adrenalin still induced them. Beattie, Brow and Long¹⁴ found that they could be prevented by section of the hypothalamus so long as the adrenal medulla was inactive. It is possible that in patients who display the type of paroxysmal tachycardia under consideration the heart is for some unknown reason unusually susceptible to sympathetic stimulation as it appears to be in the early stages of chloroform anesthesia.

Paroxysmal tachycardia of the classical type may usually be recognized from the patient's description of the sudden onset and termination of the attacks. Where the attacks are short and frequent and are preceded and followed by high grade extrasystolic arrhythmia, this is no longer possible and it is not easy to determine the true nature of the difficulty unless the patient is seen during an attack.

Quinidine may be regarded as a specific remedy in this disorder in the same sense as digitalis is so regarded in auricular fibrillation; i. e., the benefit derived by the patient is comparable in the two cases. In some instances small doses of this drug completely prevent the occurrence of attacks and enable the patient to return to his customary mode of life. In others, doses that are easily tolerated when taken over long periods of time are not sufficient to prevent attacks altogether, but seem to decrease their frequency and severity. These effects of quinidine are not, however, peculiar to the type of paroxysmal ventricular tachycardia described in this article; similar results occur in all types of paroxysmal ventricular tachycardia with the possible exception of the type that occurs in digitalis intoxication.

Certain features of the cardiac mechanism in the cases described are worthy of brief comment. In Case 1 there was evidently some region within the junctional tissues that was capable of conducting impulses from auricles to ventricles, but not in the reverse direction. During the paroxysms of ventricular tachycardia the sinus node continued to function as auricular pacemaker. In some of the shorter attacks the auricular complexes could be identified without difficulty; in the longer attacks this was not possible, but the frequent absence of a postparoxysmal pause when the termination of the abnormal rhythm was recorded indicates that the auricular rhythm was not disturbed by the ventricular tachycardia. The more or less regular occurrence in many of the records of isolated ventricular complexes transitional in form between the paroxysmal complexes and the complexes of supraventricular origin strongly suggests that from time to time during the paroxysms impulses of sinus origin reached the ventricles. The unidirectional block in the junctional tissues was not due to a general depression of atrioventricular conduction with a slightly greater depression of conduction from ventricles to auricles than of conduction in the opposite direction. When an auricular tachycardia occurred during a ventricular paroxysm and the auricular rate exceeded the ventricular the ventricles responded to the auricles, and there was no indication that conduction in the forward direction was in any way subnormal (Fig. 3). In Case 2 conduction took place with equal or almost equal facility in either direction; the auricles responded to the ventricles during the paroxysms, and even single ventricular extrasystoles were followed by sequential auricular beats (Fig. 5).

These cases furnish no data that enable us to come to any final decision regarding the nature of the abnormal mechanism, and a full discussion of all of the possibilities would prolong this article beyond a reasonable length. We may, however, point out a few difficulties that are encountered when an attempt is made to interpret them in terms of the views with respect to paroxysmal tachycardia that are now most widely held. If the ventricular paroxysms are attributed to circus contraction and the isolated extrasystoles are regarded as re-entrant beats, it is difficult to understand what took place when, as in Case 1 and in one of the cases described by Wenckebach and Winterberg, a portion of the ventricular muscle responded to the paroxysmal center and a portion to stimuli that descended from the auricles, or when the paroxysmal rhythm was temporarily interrupted by a more rapid rhythm of supraventricular origin (Fig. 3). If the paroxysmal rhythm was indeed a circus rhythm, one must assume that the interfering stimuli did not penetrate to the ring of muscle traversed by the re-entrant wave. This assumption places serious limitations upon the size of this ring and involves further assumptions of questionable validity regarding the rate of conduction about it or the length of the refractory period of the muscle of which it was made up. When the ectopic rhythm was interrupted temporarily, the

interfering stimuli did apparently penetrate to the ectopic center, for measurement shows that the periods of interruption are not uniformly exact multiples of the length of the paroxysmal cycle, and consequently that the abnormal rhythm was not merely submerged but was brought temporarily to an end and was reestablished when the interfering rhythm terminated.

We were unable to demonstrate by measurement that the interval separating two successive ventricular extrasystoles occurring during the period immediately preceding the onset or immediately following the termination of a paroxysm was uniformly an exact multiple of the paroxysmal cycle length even when the extrasystoles were occurring regularly. When two paroxysms were separated by a single beat of sinus origin, the interval which separated the last beat of one paroxysm from the first beat of the other was not found to be an exact multiple of the length of the paroxysmal cycle. It would appear, therefore, that the paroxysmal center did not function continuously throughout the period of abnormal heart action and that the extrasystolic arrhythmia occurring between paroxysms cannot be regarded as due to parasystole with exit-block unless it is assumed that the paroxysmal rate was not the full rate of the paroxysmal center.

SUMMARY

There is a type of paroxysmal ventricular tachycardia in which the abnormal mechanism is induced by emotion and exertion. The attacks may be long, but more often short attacks separated by periods of extrasystolic arrhythmia occur in rapid succession. In the majority of the cases there is no other evidence of cardiac disease. Patients with this disorder are usually seriously incapacitated. Small doses of quinidine are often strikingly beneficial but do not always prevent the occurrence of attacks.

In one of the cases studied by the authors a long paroxysm of ventricular tachycardia was frequently interrupted temporarily by short attacks of paroxysmal auricular tachycardia.

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FURTHER OBSERVATIONS ON THE HEART IN OLD AGE. A POSTMORTEM STUDY OF 381 PATIENTS AGED SEVENTY YEARS OR MORE

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IN a previous publication, one of us² presented a clinical study of the hearts of 700 aged persons, and brought forth evidence to show that most aged persons, even in the presence of heart disease, possess hearts of unusual quality. The heart that allows life to continue to advanced age is an organ of rare integrity.

Statistical studies have clearly shown that the greatest mortality from heart disease occurs between the fiftieth and the seventieth years of life, and it appears that persons who have survived this period are more likely ultimately to succumb to other diseases, such as carcinoma, pneumonia, or nephritis. It thus seems that nature selectively eliminates the "cardiac group" in the prime of life, and the survivors are largely destined to continue life with relatively adequate cardiovascular systems, awaiting deterioration from other causes.

THE PRESENT STUDY

It seemed desirable to augment the previous study by analysis of the records of necropsy of aged patients, with the idea of obtaining the following information: quantitative data on the incidence and degree of coronary, aortic, and valvular sclerosis; comparative data regarding cardiac weights with reference to hypertension and other factors concerned with cardiac hypertrophy, and the incidence of pathological changes other than arteriosclerosis.

Material.—We studied the postmortem records for a period of ten years, selecting all patients of seventy years of age and older, regardless of the cause of death. We obtained 381 cases among 5,751 postmortem records, an incidence of 6.6 per cent. The age of the patient was the only basis on which selection was made.

In order to show that we appreciate the fact that our material may differ from that in other localities we quote from the previous publication. "It must be acknowledged that the results of critical analysis of this selected material are not entirely comparable to those that might be derived from a similar number of cases, of patients of the same ages as those selected, taken from the general population or from other limited fields of the general population. It must be assumed that the majority of aged patients who seek medical advice at a clinic which is more or less distant from their homes have ailments that may not exist to the same degree and extent among patients in other groups."

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Age.—In order to simplify the presentation of statistical data, the cases were apportioned into age groups of five years, with the exception of those which occurred in the tenth decade of life. Only four patients were ninety years of age or older, and these were considered in one age group. More than half (59.4 per cent) of the patients were between the ages of seventy and seventy-four years (Table I). The incidence naturally diminished as the later age periods were reached. There were sixty patients (15.7 per cent) eighty years of age or older.

Sex.—There was a marked predominance of males (Table I), the incidence being 5 to 1. The high incidence of males was in part influenced, as in the previous study, by a relatively large number of old men suffering from hypertrophy of the prostate gland.

TABLE I
INCIDENCE BY AGE AND SEX

AGE GROUP, YEARS	CASES	PER CENT	MALES		FEMALES	
			CASES	PER CENT	CASES	PER CENT
70 to 74	226	59.4	187	82.7	39	17.3
75 to 79	95	24.9	82	86.3	13	13.7
80 to 84	35	9.2	22	62.9	13	37.1
85 to 89	21	5.5	15	71.4	6	28.6
90 to 99	4	1.0	2	50.0	2	50.0
Total	381	100	308	80.8	73	19.2

Coronary Sclerosis.—Some degree of coronary sclerosis was present in all the cases, although great difference in the degree of involvement was noted. The degree of involvement was graded from 1 to 4, the former indicating little arterial change, whereas the latter denoted very extensive and advanced atherosclerosis. It is interesting to note that in ten cases (2.6 per cent) changes in the coronary arteries were scarcely perceptible (Table II); these cases were in the first age group, seventy to seventy-four years. From the averages in Table II, it is apparent that the coronary arteries of the majority of aged patients (276 cases, 72.5 per cent) reveal moderate to advanced (grades 2 to 4) atherosclerosis. This is a significant fact, and one that finds very definite application in the consideration of aged patients, not only from the standpoint of medical problems but particularly when the question of surgical intervention arises. No definite correlation between the various age groups and the degree of coronary sclerosis was evident in this study.

Aortic Sclerosis.—Fairly definite parallelism between the degree of coronary sclerosis and of aortic sclerosis occurred in this group of patients (Table III), although rather wide variations occurred. Thus,

TABLE II
DEGREE OF CORONARY SCLEROSIS (381 CASES)

AGE GROUP, YEARS	GRADE 1				GRADE 2				GRADE 3				GRADE 4			
	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES
70 to 74	73	32.3	61	12	94	41.6	74	20	44	19.5	38	6	15	6.6	14	1
75 to 79	24	25.3	20	4	42	44.2	38	4	25	26.3	21	4	4	4.2	3	1
80 to 84	5	14.3	3	2	14	40.0	8	6	11	31.4	8	3	5	14.3	3	2
85 to 89	3	14.3	2	1	9	42.8	7	2	9	42.9	6	3	0	0	0	0
90 to 99	0	0	0	0	1	25.0	0	1	2	50.0	1	1	1	25.0	1	0
Total and percentage	105	27.5	86	19	160	42.0	127	33	91	23.9	74	17	25	6.6	21	4

TABLE III
DEGREE OF AORTIC SCLEROSIS (381 CASES)

AGE GROUP, YEARS	GRADE 1				GRADE 2				GRADE 3				GRADE 4			
	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES	TOTAL CASES	PER CENT	MALES	FEMALES
70 to 74	56	24.8	46	10	103	45.5	90	13	61	27.0	48	13	6	2.7	3	3
75 to 79	17	17.9	16	1	47	49.4	41	6	29	30.6	24	5	2	2.1	1	1
80 to 84	1	2.9	1	0	15	42.8	10	5	18	51.4	10	8	1	2.9	1	0
85 to 89	2	9.6	1	1	5	23.8	4	1	12	57.1	8	4	2	9.5	2	0
90 to 99	0	0	0	0	1	25.0	1	0	2	50.0	1	1	1	25.0	0	1
Total and percentage	76	20.0	64	12	171	44.9	146	25	122	32.0	91	31	12	3.1	7	5

moderate to advanced aortic sclerosis occurred in 305 cases (80 per cent). As in the case of coronary sclerosis, no definite relationship between the various age groups and the degree of aortic sclerosis was observed.

Valvular Sclerosis.—Varying degrees of valvular sclerosis occurred in 353 cases (92.7 per cent). As would be anticipated, the valves of the left side of the heart were involved much more frequently than were those of the right side. The mitral and aortic valves were sclerosed to varying degrees in 304 cases (86.1 per cent), whereas the tricuspid and pulmonic valves were involved in only forty-nine cases (13.9 per cent), a ratio of 6 to 1.

Curiously, the frequency of sclerosis of the mitral valve (157 cases, 44.5 per cent) slightly exceeded that of sclerosis of the aortic valve (147 cases, 41.6 per cent). The degree of sclerosis of the mitral valve was slight (grade 1) in eighty-eight cases (56 per cent); moderate (grade 2) in sixty-four cases (40.8 per cent), and marked (grade 3 to 4) in only five cases (3.2 per cent). The degree of sclerosis of the aortic valve was more marked. The sclerosis was slight (grade 1) in fifty-eight cases (39.5 per cent), moderate (grade 2) in sixty-seven cases (45.6 per cent), and marked (grade 3 to 4) in twenty-two cases (14.9 per cent).

The tricuspid valve was the seat of sclerosis in thirty-two cases (9.1 per cent), whereas the pulmonic valve was involved in only seventeen cases (4.8 per cent). The degree of sclerosis of the tricuspid valve was as follows: slight involvement (grade 1) nineteen cases (59.4 per cent); moderate involvement (grade 2) twelve cases (37.5 per cent); and marked involvement (grade 3 to 4) only one case (3.1 per cent). In the pulmonic valve, the degree of sclerosis was slight (grade 1) in nine cases (52.9 per cent); moderate (grade 2) in seven cases (41.2 per cent); and marked (grade 3) in only one case (5.9 per cent).

No constant correlation between the degree of valvular sclerosis and the various age groups could be determined.

Associated Cardiac Disease Other Than Arteriosclerosis.—We were interested in determining the incidence of associated cardiac disease in this group of aged patients, particularly to ascertain the frequency of lesions acquired in the earlier periods of life that did not materially interfere with cardiac function, and, in spite of their presence, permitted the patient to live to an advanced age.

Associated cardiac disease occurred in sixty-one cases (16.4 per cent). Evidence of healed cardiac infarction was found in fifteen cases; eleven of the patients died of heart failure. Acute cardiac infarction was observed in eleven cases, death in all instances ensuing soon after the onset of the attack. Evidence of old, healed endocarditis was found in fourteen cases; in one case mitral stenosis was well marked, and in three cases marked aortic stenosis with calcification occurred.

Pericarditis was present in twelve cases; chronic adherent pericarditis was found in five, chronic fibrinous pericarditis in three, and acute fibri-

nous pericarditis in four. Acute bacterial endocarditis, an incident in generalized sepsis, occurred in five cases. Only three cases of syphilitic aortitis were observed. In one case, carcinoma had metastasized to the heart.

TABLE IV

SYSTOLIC BLOOD PRESSURE OF 371 PATIENTS SEVENTY YEARS OF AGE OR OLDER

BLOOD PRESSURE, MM. OF MERCURY	AGE GROUP, YEARS										TOTAL	
	70 TO 74		75 TO 79		80 TO 84		85 TO 89		90 TO 99		CASES	PER CENT
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT		
80 to 89	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	1	0.3
90 to 99	5	100.0	0	0.0	0	0.0	0	0.0	0	0.0	5	1.3
100 to 109	11	73.3	2	13.3	1	6.7	0	0.0	1	6.7	15	4.1
110 to 119	15	51.7	9	31.0	4	13.8	1	3.5	0	0.0	29	7.8
120 to 129	19	59.4	8	25.0	3	9.4	1	3.1	1	3.1	32	8.6
130 to 139	30	56.6	16	30.2	4	7.5	3	5.7	0	0.0	53	14.3
140 to 149	36	69.2	10	19.2	4	7.8	1	1.9	1	1.9	52	14.0
150 to 159	32	61.5	11	21.1	4	7.8	5	9.6	0	0.0	52	14.0
160 to 169	18	47.3	13	34.2	5	13.1	1	2.7	1	2.7	38	10.2
170 to 179	19	63.3	8	26.7	1	3.3	2	6.7	0	0.0	30	8.1
180 to 189	15	65.3	3	13.0	3	13.0	2	8.7	0	0.0	23	6.2
190 to 199	5	45.4	4	36.4	1	9.1	1	9.1	0	0.0	11	2.9
200 to 209	6	46.2	3	23.1	1	7.6	3	23.1	0	0.0	13	3.6
210 to 219	4	50.0	4	50.0	0	0.0	0	0.0	0	0.0	8	2.2
220 to 229	1	20.0	1	20.0	3	60.0	0	0.0	0	0.0	5	1.3
230 to 239	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	0.3
240 to 249	2	66.7	1	33.3	0	0.0	0	0.0	0	0.0	3	0.8
Total	218		93		35		21		4		371	100.0
Mean blood pressure	117.3		118.7		119.8		125.0		107.0			
Percentage more than 140 mm.	63.3		62.3		62.8		76.1		50.0			

Blood Pressure.—Records of blood pressure were available for study in 371 cases (97.3 per cent). In numerous cases the average of several readings was accepted, whereas in others only single readings were recorded.

In the previous study, in which readings of blood pressure of 700

aged patients were investigated, it was determined that 74.5 per cent had systolic blood pressure of 140 mm. or more, that 40.3 per cent had diastolic blood pressure of 90 mm. or more, and that 69.6 per cent had pulse pressures of 60 mm. or more. The range of the mean pressure, or the arithmetic average of the systolic and diastolic pressures, was 109 to 127.8 mm. These figures indicated a tendency to readings usually seen in hypertension among older patients.

TABLE V

DIASTOLIC BLOOD PRESSURE OF 371 PATIENTS SEVENTY YEARS OF AGE OR OLDER

BLOOD PRESSURE, MM. OF MERCURY	AGE GROUP, YEARS										TOTAL	
	70 TO 74		75 TO 79		80 TO 84		85 TO 89		90 TO 99			
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	CASES	PER CENT
40 to 49	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	1	0.3
50 to 59	5	45.5	2	18.2	3	27.2	1	9.1	0	0.0	11	2.9
60 to 69	22	59.5	7	18.9	4	10.8	3	8.1	1	2.7	37	9.9
70 to 79	57	61.3	29	31.2	4	4.3	3	3.2	0	0.0	93	25.1
80 to 89	60	65.3	16	17.4	10	10.8	4	4.3	2	2.2	92	24.8
90 to 99	37	50.7	21	28.8	8	10.9	6	8.2	1	1.4	73	19.7
100 to 109	20	57.1	11	31.4	1	2.9	3	8.6	0	0.0	35	9.4
110 to 119	10	58.8	4	23.5	3	17.7	0	0.0	0	0.0	17	4.6
120 to 129	6	75.0	1	12.5	1	12.5	0	0.0	0	0.0	8	2.2
130 to 139	1	33.3	1	33.3	1	33.3	0	0.0	0	0.0	3	0.8
140 to 149	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	0.3
Total	218		93		35		21		4		371	100.0
Mean blood pressure	117.3		118.7		119.8		125.0		107.0			
Percentage more than 90 mm.	33.9		40.8		40.0		47.6		25.0			

In the present study (Table IV), slightly lower averages were obtained, influenced perhaps to some degree by inclusion of patients of a younger age group, seventy to seventy-four years. Two hundred thirty-six patients of the 371 (63.6 per cent) had systolic blood pressure of 140 mm. or more. Of the patients with systolic blood pressure of 140 mm. or more, 196 (83 per cent) were found to be between the ages of seventy and seventy-nine years, inclusive. Thirty patients (13.2 per cent) had systolic blood pressure of 200 mm. or more.

The mean blood pressure for the various age groups can be read on

Tables IV, V and VI. No constant correlation between elevation of systolic and of diastolic blood pressure was apparent. Only 137 patients (36.9 per cent) had diastolic blood pressure of 90 mm. or more. The diastolic blood pressure ranged from 60 to 120 mm. in 219 cases (59 per cent) (Table V). Readings of pulse pressure of 60 mm. or more occur-

TABLE VI
PULSE PRESSURE OF 371 PATIENTS SEVENTY YEARS OF AGE OR OLDER

PULSE PRESSURE OF 371 PATIENTS SEVENTY YEARS OF AGE												
BLOOD PRESSURE, MM. OF MERCURY	AGE GROUP, YEARS										TOTAL	
	70 TO 74		75 TO 79		80 TO 84		85 TO 89		90 TO 99		CASES	PER CENT
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT		
10 to 19	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3
20 to 29	2	50.0	1	25.0	0	0.0	1	25.0	0	0.0	4	1.0
30 to 39	12	66.7	4	22.2	2	11.1	0	0.0	0	0.0	18	4.8
40 to 49	30	62.5	11	22.9	4	8.3	1	2.1	2	4.2	48	12.9
50 to 59	45	58.4	18	23.4	9	11.7	4	5.2	1	1.3	77	20.7
60 to 69	42	59.1	18	25.4	8	11.3	3	4.2	0	0.0	71	19.4
70 to 79	32	64.0	13	26.0	4	8.0	1	2.0	0	0.0	50	13.4
80 to 89	25	56.8	10	22.7	2	4.6	6	13.6	1	2.3	44	11.8
90 to 99	18	75.0	5	20.8	1	4.2	0	0.0	0	0.0	24	6.5
100 to 109	7	41.2	5	29.4	2	11.8	3	17.6	0	0.0	17	4.6
110 to 119	2	15.4	7	53.8	3	23.1	1	7.7	0	0.0	13	3.5
120 to 129	1	50.0	1	50.0	0	0.0	0	0.0	0	0.0	2	0.5
130 to 139	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3
140 to 149	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
150 to 159	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	0.3
Total	218		93		35		21		4		371	100.0
Mean blood pressure	117.3		118.7		119.8		125.0		107.0			
Percentage more than 60 mm.	58.7		63.4		57.1		71.4		25.0			

red in 223 cases (60.1 per cent). In the majority of the cases (316, — 84.6 per cent) the pulse pressure ranged between 40 to 100 mm. (Table VI).

Low blood pressure occurred infrequently. Readings of systolic blood pressure of less than 120 mm. were recorded in only fifty cases (13.4 per cent), and readings of diastolic blood pressure below 70 mm. were found

in forty-nine cases (13.2 per cent). Studies of blood pressure in this series of aged patients, like those in the previously reported series, clearly indicate the tendency for hypertensive readings to occur.

Weights of the Hearts.—The weights of the hearts in 376 cases (98.5 per cent) were suitable for study. The normal cardiac weight for the individual patient was estimated, utilizing the height-body-weight method of Smith. In any case in which marked loss of body weight had oc-

TABLE VII
ANALYSIS OF WEIGHTS OF HEARTS IN 376 CASES

PERCENTAGE INCREASE OF WEIGHT OVER ESTIMATED NORMAL	RANGE OF INCREASE OVER ESTI- MATED NORMAL, GM.	CASES	PER CENT
0	0	108	28.7
3 to 9	8 to 34	52	13.8
10 to 19	27 to 78	66	17.6
20 to 29	57 to 185	56	14.9
30 to 39	77 to 143	24	6.4
40 to 49	104 to 188	23	6.1
50 to 59	96 to 238	18	4.8
60 to 69	157 to 250	11	2.9
70 to 79	198 to 331	10	2.7
80 to 89	251 to 305	2	0.5
90 to 99	227 to 278	3	0.8
100 to 109	379 to 384	2	0.5
110 to 119	407	1	0.3

curred prior to death, as in cachexia of carcinoma, the normal weight for that patient was utilized. We are aware that in the presence of marked loss of body weight some loss in cardiac weight occurs, and that this loss is in no way proportionate to the loss in body weight, but it is impossible to ascribe accurate quantitative values to the loss of cardiac weight. Thus, some degree of error enters into our computations which, however, is probably constant throughout the series.

It is interesting to note that 268 aged persons (71.3 per cent) concerned in this study had varying degrees of cardiac hypertrophy (Table VII). However, if we exclude slight increases in cardiac weight, that is, increases of 9 per cent or less, we still record 216 cases (57.5 per cent), or approximately two-thirds of the series. Cardiac hypertrophy was marked in a fourth of the cases; the estimated increase in cardiac weight exceeded 50 per cent in forty-seven cases (12.5 per cent).

The excess cardiac weights were all readily explained by the presence

of such factors as hypertension, aortic stenosis, adherent pericarditis, healed cardiac infarction, and so forth.

No correlation between cardiac weights and the various age groups as employed in this study could be made (Table VIII). Patients with marked cardiac hypertrophy were irregularly interspersed among all age groups. Likewise, there were no striking differences in cardiac weights of the two sexes.

TABLE VIII
WEIGHTS OF HEARTS ACCORDING TO AGE GROUPS

AGE GROUP, YEARS	TOTAL CASES	CARDIAC HYPERTROPHY					
		CASES	PER CENT	PERCENTAGE INCREASE OF WEIGHT OVER ESTIMATED NORMAL	RANGE OF INCREASE OVER ESTIMATED NORMAL, GM.	HEARTS OF NORMAL WEIGHT	PERCENTAGE OF HEARTS OF NORMAL WEIGHT
70 to 74	224	160	71.4	3 to 102	8 to 379	64	28.6
75 to 79	94	63	67.0	3 to 110	10 to 407	31	33.0
80 to 84	34	28	82.3	3 to 68	12 to 185	6	17.7
85 to 89	21	14	66.7	11 to 59	34 to 205	7	33.3
90 to 99	3	3	100.0	28 to 70	78 to 263	0	0.0

In 175 cases, the clinical history and examination, as well as necropsy, failed to reveal findings pertinent to the production of cardiac hypertrophy. In eighty-eight of these cases (50.2 per cent), the actual and the estimated cardiac weights were in perfect agreement (Table IX).

TABLE IX
CARDIAC WEIGHTS IN CASES IN WHICH NO APPARENT CAUSE FOR HYPERTROPHY WAS DETERMINED (175 CASES)

PERCENTAGE INCREASE OF WEIGHT OVER ESTIMATED NORMAL	RANGE OF WEIGHT OVER ESTIMATED NORMAL, GM.	CASES	PER CENT
0	0	88	50.2
2 to 9	8 to 34	33	18.8
10 to 19	33 to 78	29	16.6
20 to 29	57 to 97	17	9.8
30 to 39	70 to 126	4	2.3
50 to 59	136 to 185	4	2.3

However, in fifty-four cases (31 per cent) the actual weights of the hearts exceeded the estimated normal from 10 to 55 per cent. The most probable explanation of the cardiac hypertrophy in these cases exists in the presence of previous hypertension, which disappeared at the close of the patient's life. There is little doubt that hypertension may spon-

taneously vanish, frequently leaving a hypertrophied heart as a relic of its former existence. This study and the former study of Smith do not indicate that there is increase in the weight of the heart in old age, except such as occurs in the presence of disease.

Causes of Death.—Analysis of the causes of death in this series clearly illustrates the character of the material, and indicates that the cases represent a typical group of aged patients.

Carcinoma led the death list with ninety-three cases, and pneumonia was next with sixty-nine cases. Pylonephritis occurred in forty-nine cases, whereas death from heart disease occurred in forty-eight cases. The deaths from cardiac disease will be analyzed more fully.

Uremia and sepsis occurred in nineteen cases, respectively; death due to trauma and to pulmonary embolism in seventeen cases; cerebral hemorrhage in thirteen cases; peritonitis in eleven cases; arteriosclerosis in eight cases; pernicious anemia in four cases; lymphatic leucemia in three cases; ulcerative colitis and sarcoma in two cases, respectively. The following diseases were represented by one case each: diabetes mellitus, adenomatous goiter with hyperthyroidism, hepatic cirrhosis, ruptured thoracic aneurysm, intestinal obstruction, Hodgkin's disease, and tuberculosis.

In the forty-eight cases in which death was attributable to the heart, hypertensive heart disease was present in fourteen cases, cardiac failure consequent to healed cardiac infarction in eleven cases, acute cardiac infarction in eleven cases, coronary sclerosis with angina pectoris in seven cases, aortic stenosis in three cases, syphilitic aortitis in one case, and chronic adherent pericarditis in one case.

COMMENT AND SUMMARY

As in the previous publication² on the heart of aged persons, this study likewise leads to the conclusion that the hearts of persons who live to old age, in the majority of cases, are of remarkable quality. This finds confirmation in the fact that only forty-eight patients (12.6 per cent) died of heart disease.

This study of the heart comprised 381 patients ranging in age from seventy to ninety-nine years who came to necropsy. Fifty-nine and four-tenths per cent of the patients were between the ages of seventy and seventy-four years, whereas 15.7 per cent were eighty years or older. The ratio by sexes was five men to one woman. Varying degrees of coronary sclerosis occurred in all cases, but the involvement was moderate to advanced in 72.5 per cent of them. Likewise, aortic sclerosis was a constant finding, but existed in from moderate to marked degree in 80 per cent of the cases. Sclerosis of the valves occurred in 92.7 per cent of the cases. Cardiac disease, other than arteriosclerosis, was present in 16.4 per cent of the cases. The readings of blood pressure in 371 cases

indicated a tendency to hypertension. The causes of death in this group of aged patients were diverse. Only 12.6 per cent died of heart disease. This clearly shows the suitability of the material for a study of this nature.

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RHEUMATIC HEART DISEASE

II. INCIDENCE AND DISTRIBUTION OF THE AGE OF DEATH*

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THE rôle of rheumatic heart disease in the causation of death was discussed in a previous communication.¹ The absolute frequency of rheumatic heart disease was estimated, and an attempt made to differentiate between the frequency of death from rheumatic heart disease, the frequency of death in which rheumatic heart disease is a contributing factor, and of death in which rheumatic heart disease is present as a non-contributing and incidental finding.

Two sets of data are essential to a study of the natural history of rheumatic heart disease: the age distribution and incidence of (a) the first infection, (b) the death of the patients. The determination of the occurrence of the first rheumatic infection, particularly of the heart, is difficult. The distribution of the age of death, however, can be determined accurately, and this knowledge is pertinent to clinical and public health problems. The present discussion is therefore concerned with that phase of the subject.

DISTRIBUTION OF THE AGE OF DEATH IN RHEUMATIC HEART DISEASE

Fig. 1 shows the age distribution in 161 of the total 164 instances of death caused directly by rheumatic heart disease and occurring in a series of 5215 consecutive necropsies performed in the Boston City Hospital between the years 1905 and 1929, inclusive. But few deaths occurred in the first decade. The death rate was distributed mainly over the second to the seventh decades. The largest number of deaths occurred in the fourth and fifth decades; but as many as 37 cases, or 23 per cent, of the total number of deaths occurred in the sixth and seventh decades. In the third decade there was a comparative but perhaps not significant decrease. This fact, that not infrequently rheumatic heart disease may be responsible for death as late as the sixth and seventh decades of life, is often not appreciated in clinical medicine.

The age of death in patients dying from rheumatic heart disease was studied in 68 additional cases in which necropsy was not performed. The diagnosis in this group of cases was based on clinical and laboratory findings. The patients were observed in the Boston City Hospital during the years 1920 to 1929. The distribution of the age of death in this group is shown in Fig. 2, and the curve is not significantly different from that of the 161 necropsied cases. These 68 cases, however, cannot be considered as representative as the necropsy series, for

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undoubtedly some cases of death from rheumatic heart disease are unrecognized in the absence of postmortem studies. Fig. 3 represents the two groups combined. The combined group, comprising 229 cases, is large enough to permit certain general conclusions concerning the distribution of the age of death in rheumatic heart disease.

Willius² reported the age distribution of death in 160 cases without necropsy examination, and Coombs³ in 98 cases with necropsy. As

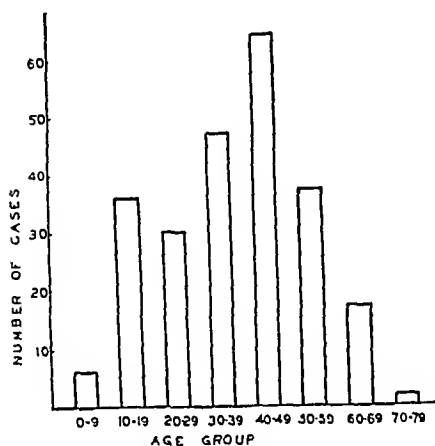


Fig. 1.

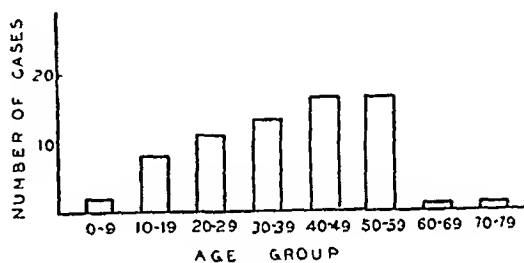


Fig. 2.

Fig. 1.—Age distribution of 161 deaths caused directly by rheumatic heart disease.

Fig. 2.—Age distribution of 68 additional cases of death from rheumatic heart disease in which necropsy was not performed.

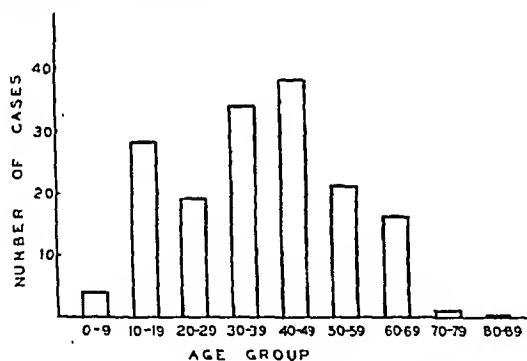


Fig. 3.—Age distribution of 161 autopsied cases of death caused directly by rheumatic heart disease and of 68 additional cases of death in which autopsy was not performed.

these authors apparently did not determine whether or not death in the respective groups was directly due to rheumatic heart disease, their figures are not comparable to those of Fig. 3.

THE AGE OF DEATH IN RHEUMATIC HEART DISEASE COMPLICATED BY SUBACUTE BACTERIAL ENDOCARDITIS AND ACUTE MALIGNANT ENDOCARDITIS

A discussion of the incidence of the age distribution of death due to rheumatic heart disease should include those cases which are complicated by subacute bacterial endocarditis and acute bacterial endocarditis.

These may be regarded as complications which ordinarily occur on the basis of an old rheumatic infection of the heart. Fig. 4 shows the age variation in the group of deaths from subacute bacterial endocarditis. This group comprises 47 cases, 35 of which gave morphological or clinical and morphological evidence of a rheumatic basis. The remaining 12 cases may also have occurred on a basis of rheumatic heart disease, but this was not noted in the postmortem records. In 6 of these cases

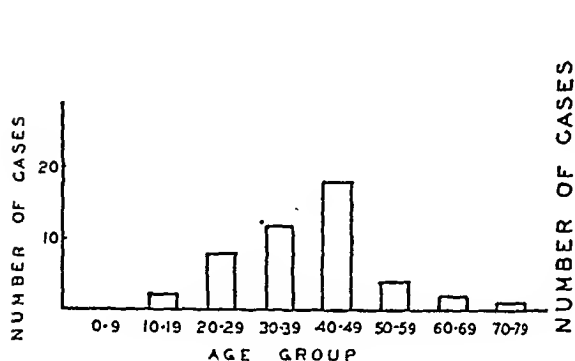


Fig. 4.

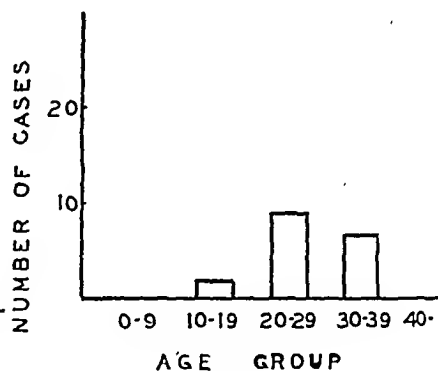


Fig. 5.

Fig. 4.—Age distribution of 47 deaths caused by subacute bacterial endocarditis.
Fig. 5.—Age distribution of 18 deaths caused by primary malignant endocarditis.

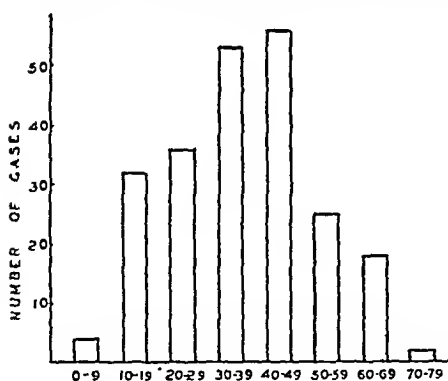


Fig. 6.

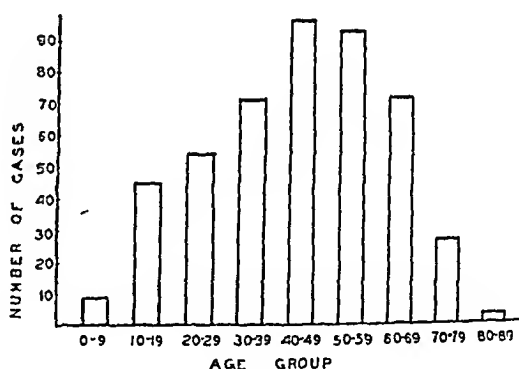


Fig. 7.

Fig. 6.—Age distribution of 226 deaths caused by rheumatic heart disease and by rheumatic heart disease combined with subacute and acute bacterial endocarditis.

Fig. 7.—Age distribution of all 467 cases in which rheumatic heart disease was present as a contributing or noncontributing factor to death.

a history of rheumatic pains and fever was obtained. Subacute bacterial endocarditis occurred at all ages from fifteen to seventy-five years. A relatively large number of cases (40 out of 47) occurred before the age of fifty years. This is somewhat in contrast to the small group of cases with acute malignant endocarditis (Fig. 5) in which all deaths occurred before the age of forty years.

Fig. 6 represents the age distribution in the group of deaths from rheumatic heart disease and rheumatic heart disease combined with subacute and acute bacterial endocarditis. Ages were available in 223 of a total of 232 of these cases. A definite accentuation of the curve occurs again between the ages of thirty and forty-nine years.

Fig. 7 shows the age distribution of all cases in which rheumatic heart disease was present, regardless of whether or not rheumatic heart disease caused death directly, contributed to it, or was present as a mere accidental finding. The character of this distribution curve is essentially the same as that representing the group of cases in which rheumatic heart disease was the cause of death (Fig. 1).

A COMPARISON OF THE AGE DISTRIBUTION IN CASES WITH RHEUMATIC HEART DISEASE WITH THAT OF THE ENTIRE NECROPSY SERIES OF 5215 CONSECUTIVE CASES

Fig. 8 shows the age distribution, expressed in percentage of the total numbers, of the 5060 available cases of the 5215 necropsy series. Curves

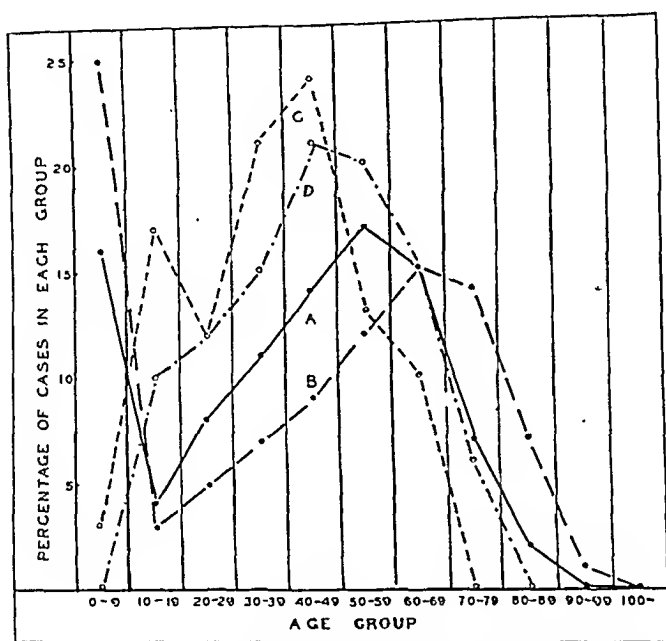


Fig. 8.—A, Percentage age distribution of 5060 consecutive deaths, Boston City Hospital (1905-1929). B, Percentage age distribution of total deaths in urban population of Massachusetts (average for years 1910, 1916, 1922, 1928). C, Percentage age distribution of 161 deaths caused directly by rheumatic heart disease. D, Percentage age distribution of all deaths (467) in which rheumatic heart disease was present.

of the age distribution of all cases with rheumatic cardiac manifestations and all cases with rheumatic cardiac death are shown on the same chart for comparison. Fig. 9 represents the same data expressed in absolute numbers. The distribution of the age of death in these 5060 cases taken from the Boston City Hospital and the average distribution reported by the United States Department of Commerce for the urban population of Massachusetts for 1910, 1916, 1922 and 1928, are indicated in Figs. 8 and 9. Although the two curves are not strictly parallel, there is a fair degree of similarity between them. The most outstanding difference is that in the hospital population the deaths predominate between the fourth and seventh decades and are relatively scarce after the seventh decade as com-

pared with the urban population. The probable explanation of this difference lies in the fact that adult and middle aged people with ailments are likely to enter the hospital for relief, while very old people are inclined to stay at home until the time of death. Notwithstanding these differences in the age distribution of the population of the Boston City Hospital and the urban population of Massachusetts, it is felt that with reservations the incidence of rheumatic heart disease in the postmortem series of the Boston City Hospital is roughly applicable to the community as a whole. The application of the age distribution in these 5060 cases to the population at large is further warranted by a comparison of the incidence of a disease such as cancer in the necropsy series with that reported by public health statistics for the entire community. The aver-

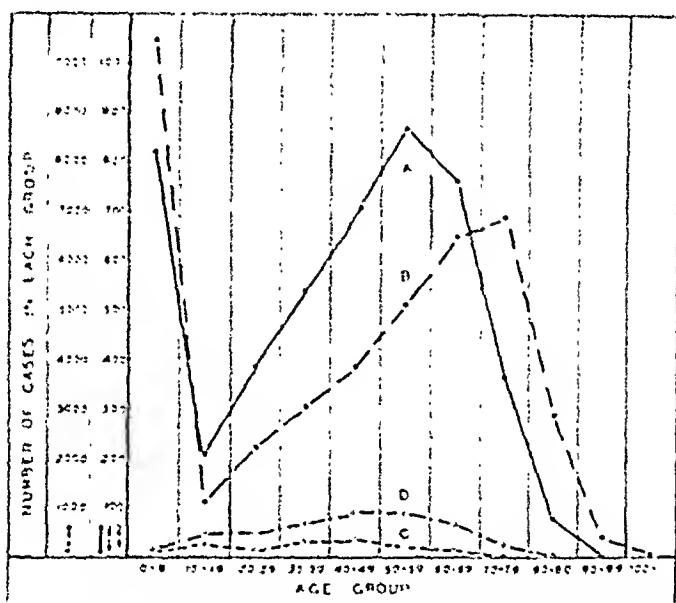


Fig. 2.—A, Age distribution of 5060 consecutive deaths, Boston City Hospital (1905-1920). B, Age distribution of total deaths in urban population of Massachusetts (average for years 1910, 1916, 1922, 1928). C, Age distribution of 161 deaths caused directly by rheumatic heart disease. D, Age distribution of all deaths (467) in which rheumatic heart disease was present.

age incidence of cancer in the cases on which necropsy examination was performed was 10.4 per cent between the years 1910 and 1928.¹ The average incidence of cancer in the urban population of Massachusetts was 5.58 per cent in 1910, 7.05 per cent in 1916, 9.12 per cent in 1922, and 10.72 per cent in 1928, with an average of 8.12 per cent for the four years. The gradual increase in the incidence of cancer is attributed to the increasing recognition of the disease rather than to its greater incidence. Hence the figures for the past decade, with an average of between 9 and 10 per cent, are comparable to the average incidence of cancer in 10.4 per cent of the population of the Boston City Hospital.

A comparative examination of the curves (Fig. 9) reveals that approximately 20 per cent of the total necropsied deaths occurring in the

second decade show some earmarks of rheumatic heart disease and that 15 per cent of all deaths in this decade are caused by rheumatic heart disease.

This strikingly high percentage is explained by the relatively small number of deaths from various causes in the second decade of life and the high incidence of the rheumatic infection in the first and second decades. Thus in 114 cases of rheumatic heart deaths (93 with necropsies and 31 without) with a positive rheumatic history, the first symptoms of the infection occurred before the age of twenty-one years in 76 cases (68 per cent). A further contributing factor is the fact that a vast majority of patients with a rheumatic infection occurring in the first decade survive to be exposed to intercurrent disease or die of rheumatic heart disease in the second decade. As indicated before, Fig. 1 shows very few rheumatic deaths in the first decade. The progressive decrease in the percentage of deaths due directly to rheumatic heart disease and the percentage of deaths associated with any degree of rheumatic heart disease is caused mainly by the progressive rise of the incidence of death of the hospital population at large during these decades. There is an apparent rise or stagnation in the seventh decades.

THE PROBABLE DISTRIBUTION OF RHEUMATIC HEART DISEASE AND RHEUMATIC HEART DEATHS IN BOSTON AND ITS VICINITY

Since the age distribution curve of the cases autopsied in the Boston City Hospital is roughly parallel to that of deaths in the population at large, the percentage of deaths from rheumatic heart disease in any given decade should be approximately the same in these two groups. By applying the percentages obtained from the Boston City Hospital figures to the vital and mortality statistics for the State of Massachusetts, one may estimate (1) what number of deaths in the population at large in any given decade may be expected to occur from rheumatic heart disease, and (2) what percentage of the total living population for that decade these probable deaths represent. Table I gives the result of such a calculation. The estimated frequency of fatal rheumatic heart disease varied between 10 to 100 per 100,000 population in 1910 and 10 to 900 in 1920 in various decades.

The frequency of rheumatic heart disease which contributed partially to death, and of that which was present only as an accidental, noncontributing finding at death cannot be estimated for the living population, since the figures representing this type of case cannot be applied statistically from the dead population of the hospital to the living community. In general, however, the statistics suggest that these milder types of rheumatic heart disease must be expected to occur among the living population many times more frequently than that degree of the disease which leads to death.

TABLE I
ESTIMATED FREQUENCY OF RHEUMATIC HEART DISEASE IN THE STATE OF MASSACHUSETTS

DECADE	DEATHS FROM RHEUMATIC HEART DISEASE AND COMPLICATIONS, BOSTON CITY HOSPITAL	TOTAL NECROPSIED DEATHS, BOSTON CITY HOSPITAL	PERCENTAGE OF DEATHS FROM RHEUMATIC HEART DISEASE, BOSTON CITY HOSPITAL	TOTAL DEATHS, STATE OF MASSACHUSETTS, 1920	TOTAL DEATHS, STATE OF MASSACHUSETTS, 1910	ESTIMATED DEATHS FROM RHEUMATIC HEART DISEASE, 1910	TOTAL LIVING POPULATION, STATE OF MASSACHUSETTS, 1920	TOTAL LIVING POPULATION, STATE OF MASSACHUSETTS, 1910	ESTIMATED PERCENTAGE FREQUENCY OF DEATHS CAUSED BY RHEUMATIC HEART DISEASE IN LIVING POPULATION, STATE OF MASSACHUSETTS, 1920	ESTIMATED PERCENTAGE FREQUENCY OF DEATHS CAUSED BY RHEUMATIC HEART DISEASE IN LIVING POPULATION, STATE OF MASSACHUSETTS, 1910
0-9	4	821	.5	12,368	16,524	63	745,587	623,732	.008	.013
10-19	32	217	14.7	1,646	1,680	243	635,669	581,521	.038	.043
20-29	36	390	9.2	3,282	3,329	303	670,967	638,451	.045	.048
30-39	53	542	9.8	3,916	4,102	383	608,343	552,030	.062	.073
40-49	56	714	7.8	4,554	4,615	357	502,111	421,075	.071	.086
50-59	25	874	2.9	6,154	5,501	176	356,776	276,455	.049	.057
60-69	18	758	2.4	7,784	7,168	185	207,845	166,241	.089	.103
70-79	2	372	.5	8,049	6,977	43	94,095	80,099	.046	.046
80-89	0	83		4,616	3,845		25,507	21,451		
90-99		0		738	603		2,278	1,896		
100-		1		16	23		46	30		
Unknown				9	40		3,132	3,435		

SUMMARY

The incidence and distribution by decades of the age of death of 5060 consecutive necropsy examinations performed in the Boston City Hospital have been analyzed. Deaths from rheumatic heart disease in 229 cases were distributed widely from the second to the fifth decades of life inclusive, the largest number of deaths occurring in the fourth or fifth decades. Of 47 cases in which subacute bacterial endocarditis was superimposed on an old rheumatic heart disease, 40 cases died before the age of fifty years. In all the 19 cases with malignant endocarditis superimposed on rheumatic heart disease death occurred before the age of forty years.

It is to be emphasized that as late as the sixth and seventh decades of life rheumatic heart disease is frequently present in patients with cardiac symptoms and signs. The evidence presented suggests that the age distribution of death of the hospital population studied is roughly parallel to that of the population at large. An estimate of the expected frequency of fatal rheumatic heart disease among the living population of the State of Massachusetts is presented. This estimated frequency of the fatal rheumatic heart disease must, however, represent but a small portion of the total prevalence of rheumatic heart disease in the living population.

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EXPERIENCES WITH THE DERMATHERM (TYCOS) IN RELATION TO PERIPHERAL VASCULAR DISEASE.

II. STUDY OF ABNORMAL CONDITIONS*

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IN A previous paper we attempted to establish the range of normal variation in skin surface temperatures and published studies on fifty normal medical students.¹ In this paper we shall present the results of our work with the dermatherm in the determination of skin surface temperatures in individuals suffering from various types of peripheral vascular disease. In some instances the cases presented were subjected to only a single series of observations to determine the nature of the skin temperature changes typical of their vascular disturbances. In other cases an attempt was made to follow rather closely the clinical progress of the case as correlated with the changes in skin temperature. In this study, as in our previous work, all determinations were made with the Tycos dermatherm which was developed by the Taylor Instrument Company in collaboration with Dr. W. J. Merle Scott of the University of Rochester Medical School.

For purposes of study we have grouped our cases as follows:

- I. General disturbances of peripheral circulation.
 - a. Aneurysm of abdominal aorta.
 - b. Arteriovenous fistula.
- II. Functional disturbances of peripheral circulation.
 - a. Raynaud's disease.
- III. Ill-defined and unclassified disturbances.
 - a. Dermatomyositis.
- IV. Diseases of veins.
 - a. Varicose ulcer.
 - b. Thrombophlebitis.
- V. Diseases of arteries.
 - a. Arteriosclerosis, diabetic hand.
 - b. Arteriosclerosis, diabetic foot.
 - c. Diabetic gangrene.
 - d. Thromboangiitis obliterans, two cases.

Under general disturbances of the peripheral circulation we consider first a case of aneurysm of the abdominal aorta.

CASE 1.—H. B. was a colored male of forty-eight years, who was admitted to the hospital through the accident ward with a complaint of pain in the back and in the left costovertebral angle. Two years prior to admission he had had a nephrectomy for this same complaint at another hospital. Aneurysm of the aorta was found at this operation, and subsequent examination of the kidney showed it to be normal.

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The patient remained well until three months prior to this admission when he again began to have attacks of sharp pain in the back radiating to the left inguinal region. The attacks were so severe that he had to quit work and go to bed. The pain was usually followed by nausea, gas, sour eructations and occasionally vomiting, and it had been associated with urinary frequency, nocturia, and dysuria. It was made worse by exercising and was partly alleviated by rest.

The patient was a well developed, somewhat undernourished colored male, aged forty-eight years. The eyes reacted to light and accommodation sluggishly. The thorax, heart and lungs were not remarkable. The blood pressure was 150/112 mm. There was a scar in the left lumbar region. There was definite pulsation in the left lumbar region extending to the costovertebral angle. The patient had a right

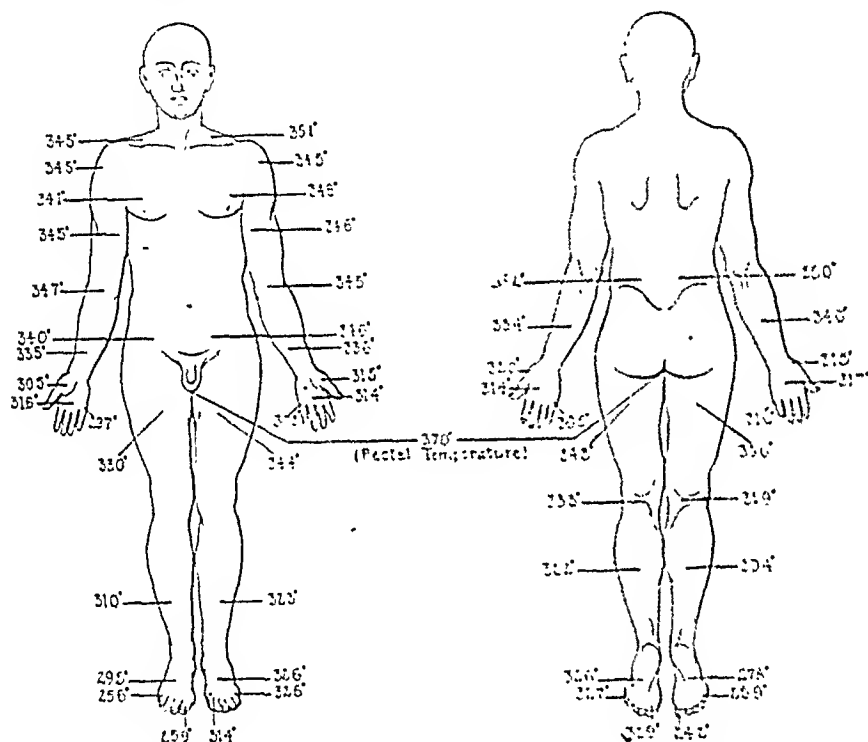


Fig. 1.—Case 1, aneurysm of the abdominal aorta.

scoliosis and tenderness over the lumbar spine. There was apparently no difference in the blood pressure in the extremities. The reflexes were physiological. Repeated urinalyses showed 20 to 30 W.B.C. per high power field; hemoglobin 85 per cent; W.B.C. 11,000; R.B.C. 4,500,000. The blood Wassermann reaction was negative on two occasions. Microscopic precipitation test negative. Blood Urea Nitrogen 16.9 mg. per 100 c.c. and 8 mg. per 100 c.c. Phenolsulphonephthalein excretion 55 per cent in two hours. X-ray films revealed nothing remarkable in the genitourinary tract. X-ray films of the spine showed the eleventh and twelfth dorsal and the first and second lumbar vertebrae to be partially destroyed. A pneumoperitoneum revealed a mass the size of a grapefruit to the left of the spine, and extending from the level of the transverse process of the ninth dorsal to the lower border of the second lumbar vertebra. Cystoscopy was done and nothing remarkable was found.

Diagnosis: Aneurysm of the aorta.

The patient's hospital course was uneventful and he was discharged. He died at home, approximately one month after leaving the hospital, and an autopsy was not done.

An examination of the dermaterm readings in this case reveals nothing of note other than a more rapid and complete development of the vasomotor gradient from the thigh downward in the right leg. (Fig. 1.) As other pulses were equal and the patient's neurological symptomatology had been practically confined to the left side, it would seem that the increased heat in the left foot was the result of pressure on the lumbar sympathetic chain giving rise to an effect analogous to Horner's syndrome.

A second case within this classification is a case of arteriovenous fistula operated upon by Dr. E. C. Cutler.

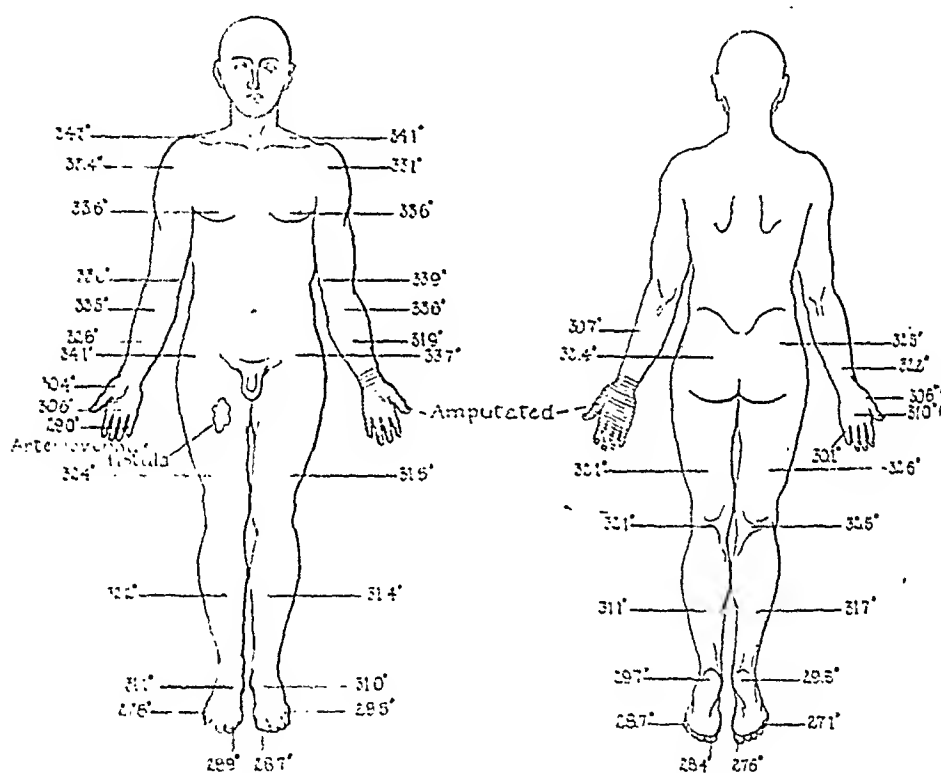


Fig. 2.—Case 2, arteriovenous fistula, preoperative.

CASE 2.—D. H. was a colored male, aged forty-nine years; he was referred to the surgical service from the medical service with the diagnosis of right femoral arteriovenous fistula close to the groin due to a wound by buckshot in 1903. The patient had been studied several times in the hospital for various other complaints. The essential fact in which we are interested is that there was a loud thrill and bruit over a large pulsating aneurysmal dilatation in the right groin. This all disappeared with obliteration of the femoral artery above the pulsation. The pulse rate dropped 40 points with obliteration of the pulsation, and the blood pressure rose about 20 points. With this there was an enlargement of the heart which also became smaller with obliteration of the pulsation. It was thought that this patient had a typical traumatic femoral arteriovenous fistula which was slowly damaging his circulation and which had already caused cardiac hypertrophy, an increased pulse rate, and presumably an increased blood flow with diminished pressure. On the grounds that with increasing age the circulatory apparatus would probably be more seriously em-

barrassed, operation was advised. Dermatherm readings were taken both before and after operation. The readings taken before operation showed a well developed vasomotor gradient in both upper and lower extremities, but no marked disparity between the two sides of the body and no evidence that the lesion in the right groin had appreciably impaired the circulation in the right leg. (Fig. 2.) At operation an extremely small arteriovenous communication with three large traumatic aneurysmal sacs in the major femoral vessel was found. The smallness of the arteriovenous communication probably explained why the patient had sustained so little cardiac damage and why the circulation in the right leg had remained good. The second series of readings taken eight days after operation showed a marked disparity in the temperature of the lower extremities. The right leg was definitely warmer than the left, averaging about 2° C. increase over the left or unaffected side. (Fig. 3.)

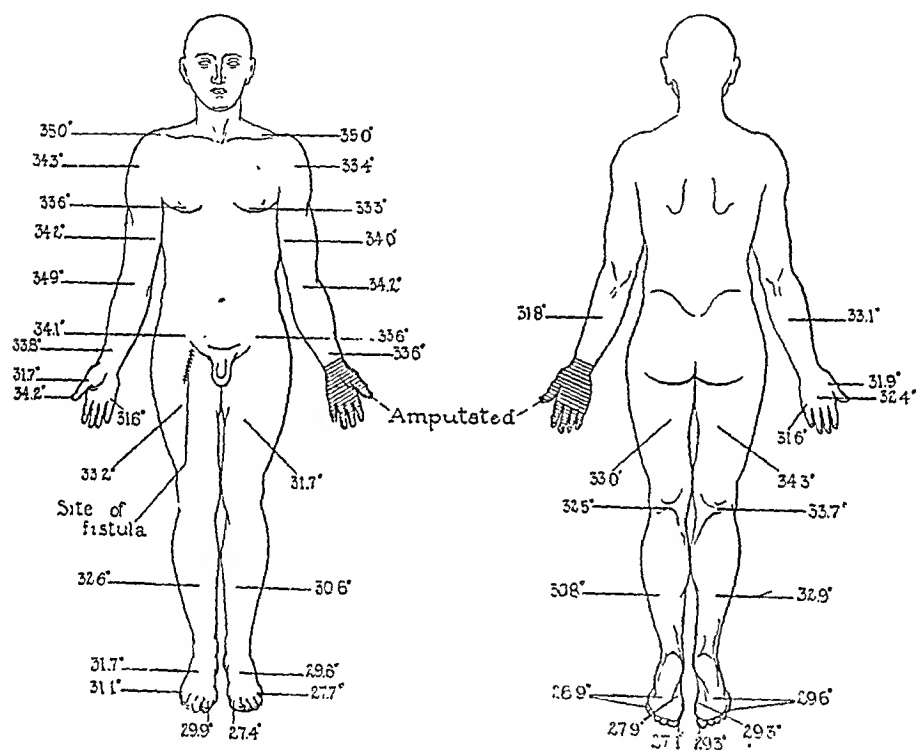


Fig. 3.—Case 2, arteriovenous fistula, postoperative.

The condition was probably not so much the result of improvement of the general circulation, nor change in the mechanical factors influencing the circulation in the right leg, as the natural sequel of a virtual periarterial sympathectomy performed in the course of stripping the adventitia and defining the vessels in the course of the operative repair.

Under the classification of functional disturbances of the peripheral circulation we have a case of Raynaud's disease.

CASE 3.—P. M., a white girl of four years, was admitted to the Lakeside Hospital with the complaint that ten days prior to admission she had developed pain in the tips of the fingers, followed shortly afterward by a bluish discoloration. The discoloration and pain had increased and the fingers had felt cold. Four days prior to admission the child was seen at University Hospital at Ann Arbor where a diagnosis of Raynaud's disease was made, and it was advised that sympathectomy be done. The child had been examined at the Elyria Clinic and given intravenous injections of

typhoid vaccine with little improvement. From the Elyria Clinic she was referred to Lakeside Hospital for gangliotectomy. The past history was essentially negative except that the child had always been susceptible to allergic reactions, and had had numerous attacks of hives. The physical examination showed the patient to be a well developed and fairly well nourished white girl of four years, not appearing acutely ill. There was an exfoliative dermatitis over the forehead. There was enlargement of the anterior cervical glands on the left side. The distal ends of the fingers of both hands were cold and showed discoloration extending slightly proximal to the first phalanx. The finger tips were not tender, but the pads showed oval areas which were practically black and appeared to be gangrenous. The radial arteries were readily palpable and the pulse was strong. The middle three toes on both feet were slightly cold, but showed no discoloration unless the child allowed the feet to

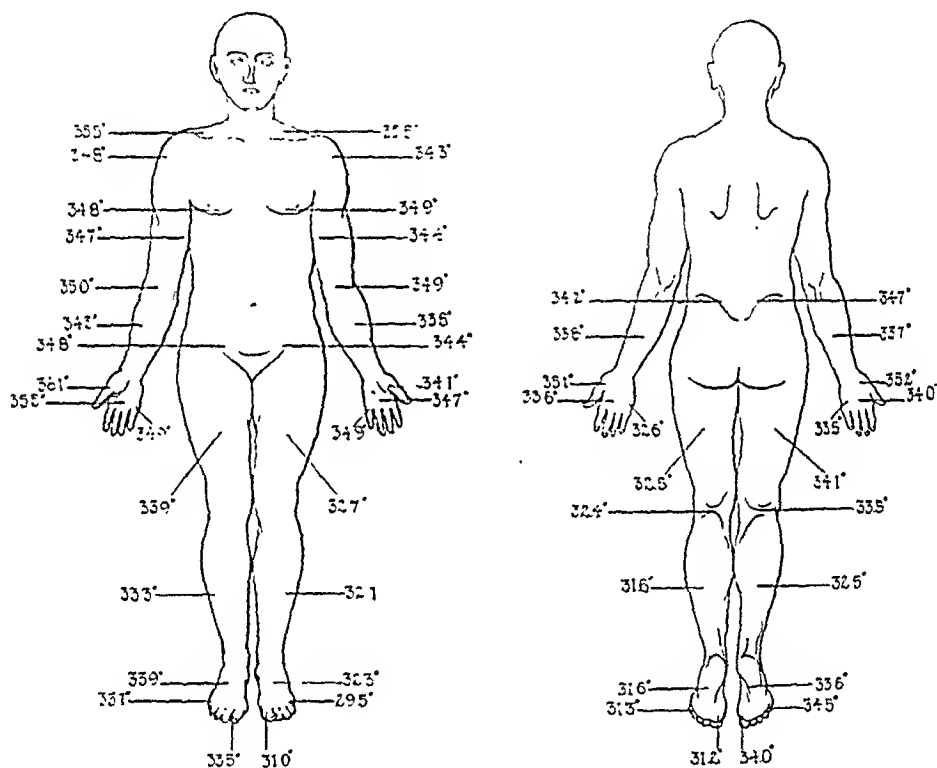


Fig. 4.—Case 3, Raynaud's disease.

hang down, when a slight purplish hue appeared. The dorsalis pedis and posterior tibial arteries were palpable in both feet.

Laboratory findings: Urine negative, W.B.C. 11,100; hemoglobin 80 per cent. The child was carefully studied while in the hospital; dermatotherm readings were made of the extremities, and x-ray plates were taken which showed no bony changes of the hands or feet and no evidence of cervical ribs. The family was advised to allow either gangliotectomy or periarterial sympathectomy to be done, but they refused and the child was discharged on release. Dermatotherm readings in this case showed an essentially normal development of the vasomotor gradient and no marked disparity between the two sides of the body except the left foot which was 1.5° to 2° colder than the right foot. (Fig. 4.) There was no apparent clinical difference in the severity of the lesions on the two sides.

CASE 4.—A rather unusual case which was diagnosed as dermatomyositis was studied. The patient was a white female of five years, who was admitted on the orthopedic service for the treatment of a contracture and flexion deformity of the

right leg. The patient was first seen in the surgical dispensary in December, 1929, with a complaint of pain in the right leg of four or five weeks' duration which had come on following a fall. At the time of the injury the mother had noticed no signs of any serious trouble; however, the child complained of pain in the thigh and leg. The physical examination in the dispensary revealed some induration about the right ankle, with slight limitation of motion at the ankle joint and a ligneous induration of the entire popliteal space, with contracture of the ham-string muscles which limited complete extension by 15 degrees. In January the patient was admitted to the hospital, and at this time the right leg was held in a position of flexion both at the hip and at the knee, and the foot also was dorsiflexed. The subcutaneous tissues and muscles of the entire right extremity felt extremely indurated and were reddened. The knee was flexed about 20 degrees, and the foot was fixed in plantar

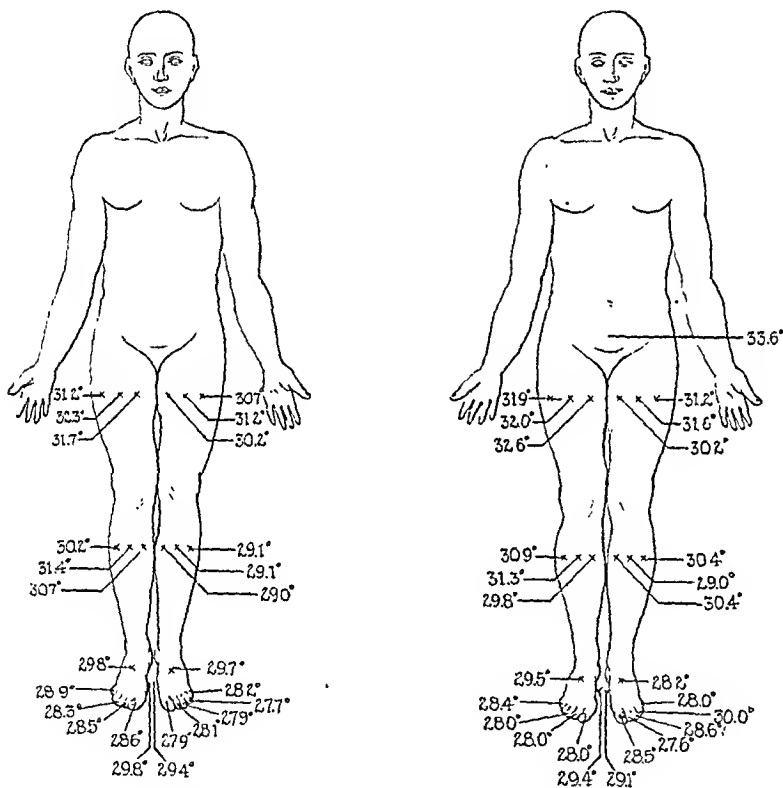


Fig. 5.—Case 4, dermatomyositis.

flexion about 15 degrees beyond a right angle. The diagnosis at that time was ischemic contracture of the lower extremity. A cast was applied and a wedging procedure begun to straighten the leg. The patient was discharged to Rainbow Hospital (convalescent hospital) in February, 1930, where an active pulmonary tuberculosis was discovered. In addition the skin over the right heel broke down due to pressure caused by wedging. An attempt was made to treat the trouble with fibrolysin, but no benefit was obtained. The condition became progressively worse and the child developed eczematoid skin lesions over the dorsum of the foot with an increase in the amount of induration in the popliteal space and along the thigh, while the toes became cold and cyanotic. The child returned to Lakeside Hospital in February, 1931, for correction of the deformity.

The physical examination revealed a fairly well developed and well nourished white female child of five years who did not appear acutely ill. The child perspired profusely, the skin being moist at all times. There were several small vesicles on

the face with a few pustules and areas of crusting. The neck showed no thyroid enlargement. There was no lymphadenopathy. The extremities and spine were normal save for the right leg which showed a contracture in the flexed position both at the hip and at the knee. There was a long band of scar tissue extending from the popliteal space to the upper part of the buttock with a similar area on the lateral surface of the right leg. The foot felt mummified; there was a red, indurated crusted lesion on the dorsum and the toes were cold and cyanotic. No pulsation of the dorsalis pedis or posterior tibial arteries could be obtained. There was no motion at the ankle joint, which was fixed in about 30 degrees plantar flexion. The knee was fixed in about 90 degrees flexion with a slight range of motion of about 5 degrees. The right extremity was uniformly smaller than the left. The neurological examination was essentially negative, but reflexes could not be demonstrated be-

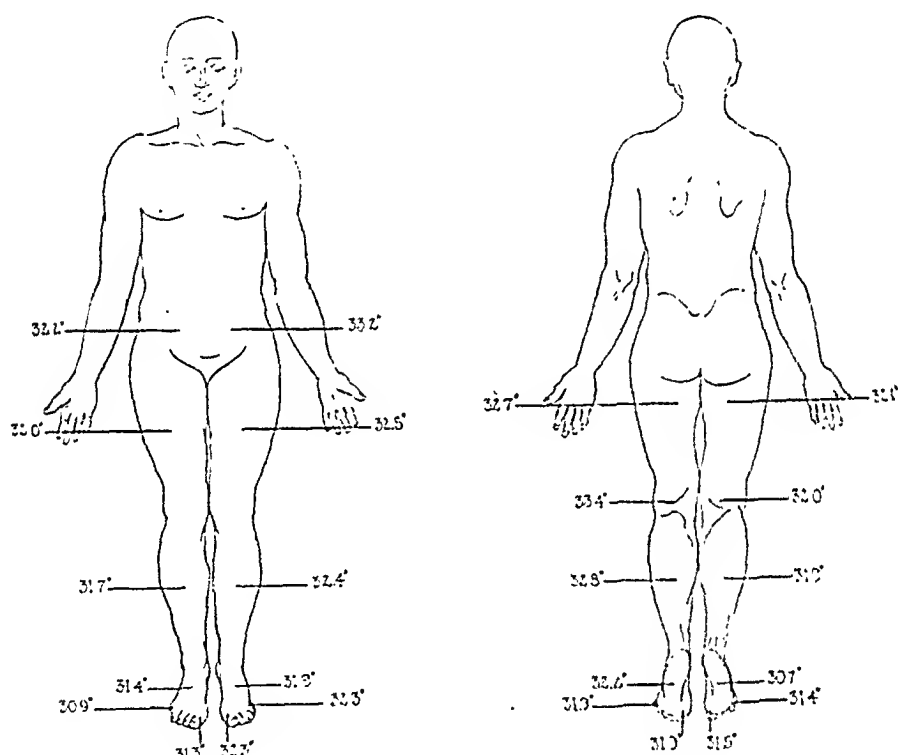


Fig. 6.—Case 5, chronic varicose ulcer of left leg.

cause of fixation of the joints by muscle contracture. There was some shortening of the right leg but the exact amount could not be determined.

The dermatherm readings of the two extremities showed an appreciable difference between the two legs. (Fig. 5.) The vasomotor gradient was very well developed, the distal portion of both extremities being quite low. There was no increase in surface temperature under gas-oxygen-ether, indicating that the impairment of circulation was secondary to a definite anatomical lesion possibly of the nature of a perivascular fibrosis rather than dependent upon vasospasm.

Diseases of veins, such as varicosities with ulceration and thrombophlebitis, were also investigated.

CASE 5.—G. B. was a colored female of fifty years, who was admitted to the hospital with the complaint of chronic varicose ulcer of the left leg. The patient had been admitted twice for the same complaint within the preceding two and one-half years, the ulcer having been skin grafted on both occasions. The leg remained

healed until about six months prior to admission when the ulcer reappeared. Local treatment was without avail, and the ulcers increased in size causing considerable disability and discomfort. The patient's left ankle swelled daily and she was forced to keep off her feet. The physical examination was essentially negative except for the left leg which had two large ulcers in the area of the former graft on the antero-lateral aspect of the lower one-third of the leg. This area was markedly contracted, its surface was tense, red, and tender, with edema of the leg above and below this area.

X-ray plates of the leg showed marked periostitis of the bone beneath the area of ulceration. The blood Wassermann examination was negative.

Dermatherm readings in this case showed a moderate development of the vaso-motor gradient with slightly increased local heat about the left foot and ankle.

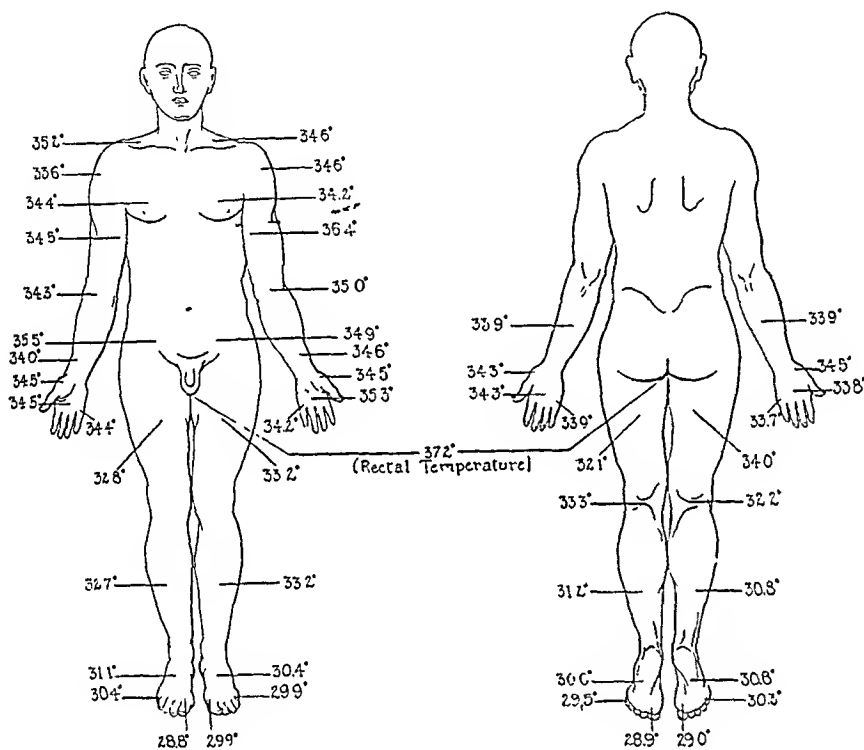


Fig. 7.—Case 6, arterial sclerosis with diabetes mellitus.

(Fig. 6.) These findings are consistent with increased vasodilatation about the inflamed and ulcerated area on the left ankle.

CASE 6.—W. S. M. was a white male of sixty-four years, who entered the hospital with a history of striking the top of the left shoulder ten days previously; following this the left arm became swollen and painful. Three days prior to admission a large inflamed area, exquisitely tender, developed on the anterior medial aspect of the left upper arm. The patient had known for nine years that he had glycosuria associated with polyuria, polydipsia and polyphagia. He had been on a limited diet under the care of his family physician for four years. During the past four years he had not adhered to any diet and had lost about 100 pounds, twenty pounds of which had been lost in the preceding three weeks.

The physical examination showed a well developed, emaciated white male of sixty-four years who appeared acutely ill. The eyes showed a moderate arcus senilis. The left side of the neck was swollen, and there was an area of brawny induration extending from the shoulder. There was a prominence over the left shoulder and

dorsalis pedis artery was palpable, the right was not. Dermatherm readings in this case showed an extremely well marked progressive drop in surface temperature below the knees, particularly on the right side. (Fig. 9.) There was a variation of 12 degrees between the highest and the lowest surface temperatures recorded which far exceeds the normal variation. The right leg and foot were two to three degrees cooler than the left which also exceeded the normal limits of variation.

CASE 9.—Our other patient, J. G., admitted on the Medical Service August 31, 1930, was a Hungarian male of fifty-five years. The present illness had begun in 1918 when he first froze his feet. In 1919 the patient began to have considerable pain in his feet and noticed that when he walked on the street his toes and feet became very painful. The pain was much worse in the winter than in the summer.

Four weeks prior to his first admission on August 21, 1930, the patient's left great toe became red, swollen and painful. The patient saw a physician who trimmed away part of the nail; after this the patient developed an ulcer. There was a great deal of pain in the left foot, especially across the dorsum.

The physical examination at the time of admission showed a well developed, slender Hungarian male of fifty-five years. The fundi revealed moderate arteriosclerotic changes. Examination of the heart showed a moderate enlargement of the left ventricle with a systolic murmur heard at the apex and over the aortic area. The blood pressure was 210/108 mm. X-ray examination showed an increased prominence of the aortic knob and a left ventricular hypertrophy. The remainder of the physical examination was negative except for the extremities. Both hands and feet showed a patchy cyanosis which was not relieved by elevation. The left great toe was swollen, reddened, the end ulcerated, the nail missing and the end of the bone exposed. There appeared to be a definite line of demarcation as if gangrene had formed. The toe was extremely tender. No dorsalis pedis could be felt in either foot, but both posterior tibials could be palpated. Pea-sized inguinal glands were palpable bilaterally. The reflexes were physiological.

Laboratory examination: urine negative; hemoglobin 110 per cent; red blood count 5,090,000; white blood count 17,000; differential normal; vital capacity 3800 c.c.; phenolsulphonephthalein excretion 40 per cent.

For several days following admission the condition of the left great toe remained virtually unchanged. On the eighth day intravenous injections of killed typhoid bacteria were begun. On the evening of this day the patient began to complain of the right leg being numb below the knee. The leg was bloodless, cold and waxlike. No pain was felt, but sensation was diminished over the lower leg and foot. The impression was that the patient had suffered an arterial thrombosis. A cradle and heat were applied and on the following day the leg had resumed its usual appearance. The patient first received fifteen million typhoid bacilli; one week later twenty million and four days later twenty-five million. At no time did the patient show extreme reaction to the injections. X-ray films in the meantime showed a definite destructive process in the distal digit of the left great toe; a diagnosis of osteomyelitis was made. Periarterial sympathectomy was advised preparatory to amputation of the toe in the hope of obtaining viable amputation flaps. The patient refused treatment, however, and left the hospital September 13, 1930.

The patient was readmitted on the Surgical Service October 22, 1930. The physical findings were essentially those of the previous admission; both hands and feet showed a patchy cyanosis which was not relieved by elevation. The left great toe was swollen and reddened; the nail was missing and the phalangeal bone was exposed. Just proximal to the nail there was a definite line of demarcation suggesting gangrene. The left foot felt warmer than the right, but the pulsation of the dorsalis pedis artery could not be felt on either side. The urine was loaded with red blood cells which cleared completely in one week. The Wassermann reaction was

negative. Blood urea nitrogen 17.5 mg. Blood sugar 132. Phenolsulphonephthalein excretion 65 per cent in two hours.

A fluctuant area of suppuration rapidly developed on the dorsum of the left foot which was incised on the third day, and approximately one ounce of pus was drained. Under treatment with hot sterile dressings and heat lamp the abscess healed rapidly. During this period red blood cells were found in the urine. On the eighth day the histamine dermal test was done on both legs. The wheal and flare were in general more marked on the right leg and were well marked as low down as the ankles on both legs.

A high ligation of the femoral vein and a periarterial sympathectomy of the left femoral artery were then performed under local anesthesia. The condition of the left leg became grossly improved and the toe was much improved. Histamine test

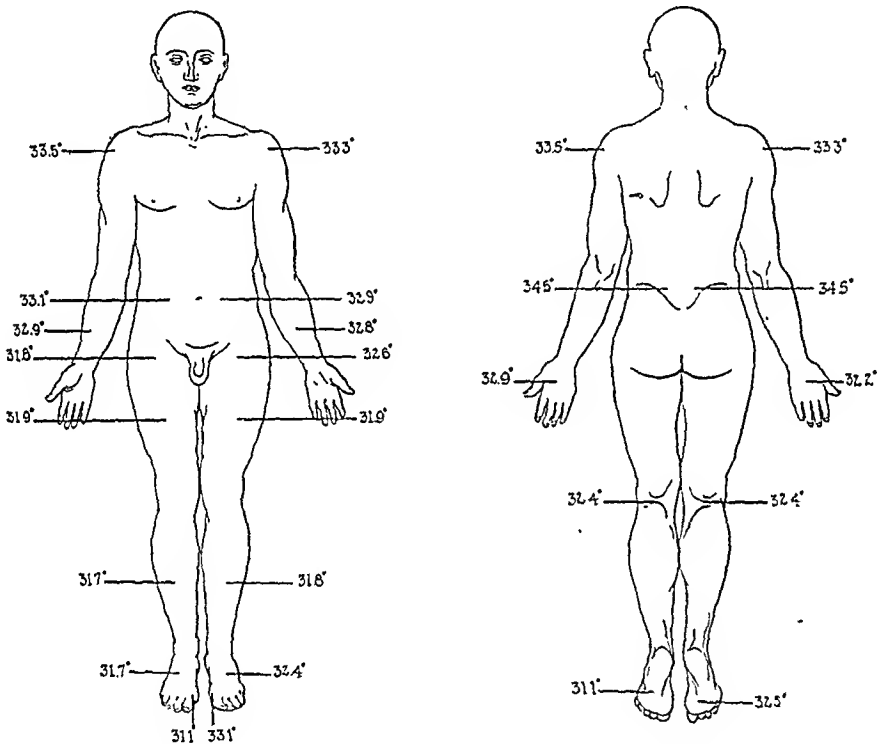


Fig. 10.—Case 9, thromboangiitis obliterans, first admission.

on the twelfth postoperative day showed a flare in seven minutes which was best at ten to twelve minutes. The leg on which the sympathectomy had been performed showed the larger flares, and flaring was well established down to the ankle. The patient was advised to undergo amputation of the left great toe because of infection, but he again refused and was discharged on November 20, 1930.

The first dermatotherm studies made in this case at the time of his admission to the Medical Service showed a temperature increase of 0.5 degree in the foot on the affected side. (Fig. 10.) The base of the great toe just proximal to the lesion was one degree Centigrade warmer than the thigh. The vasomotor gradient was not well established in the other extremity. On the second admission to the Surgical Service examination showed the entire left leg to be considerably warmer than the right (0.5 to 1.5 degrees), and the opposite leg showed an increase

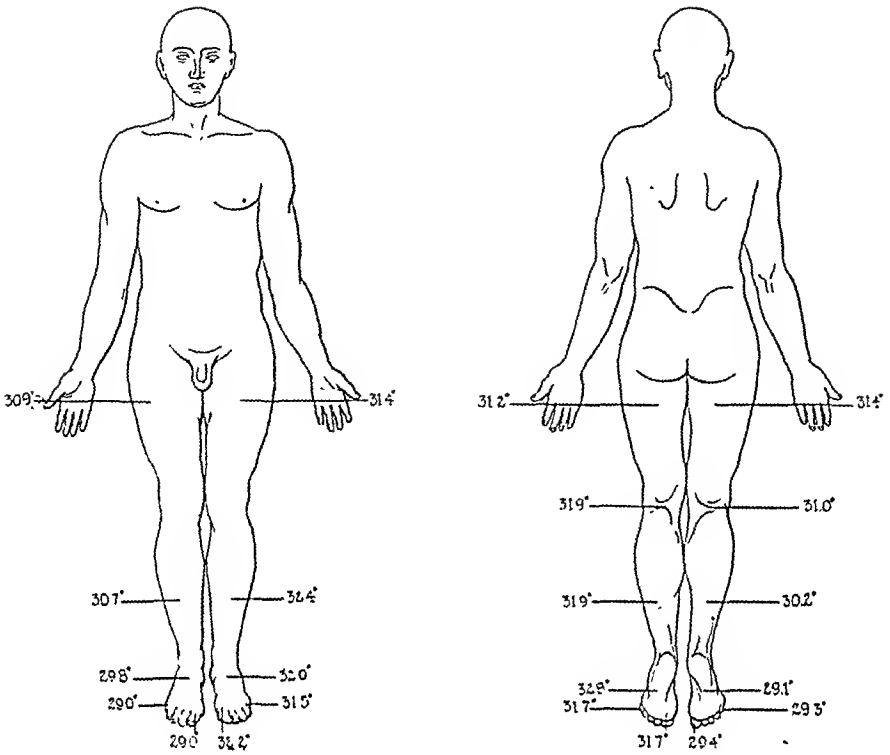


Fig. 11.—Case 9, thromboanglitis obliterans, second admission.

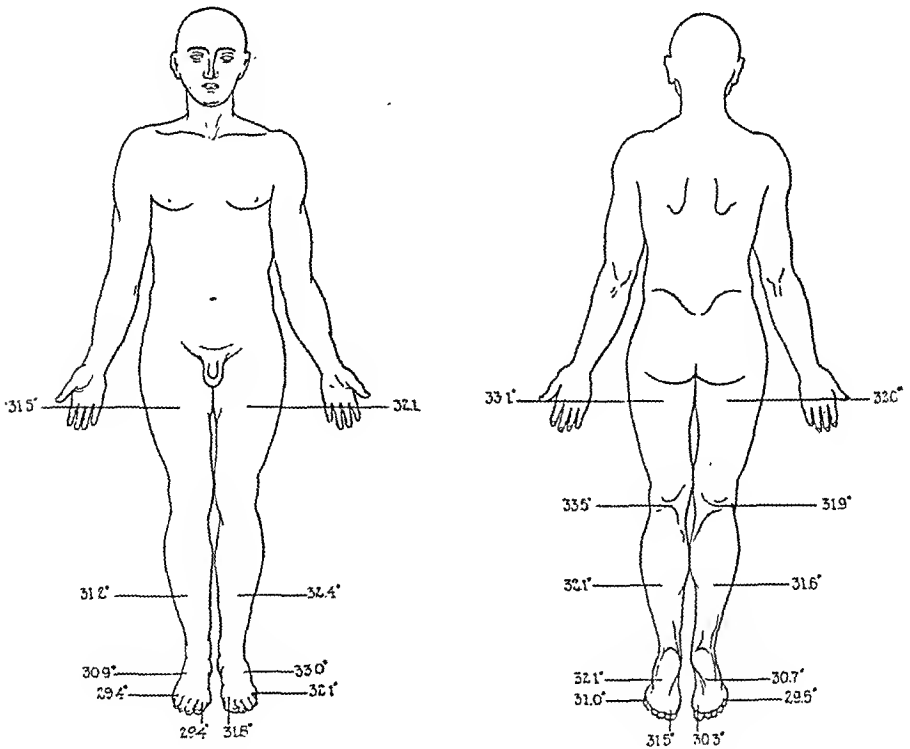


Fig. 12.—Case 9, thromboanglitis obliterans, seventh postoperative day.

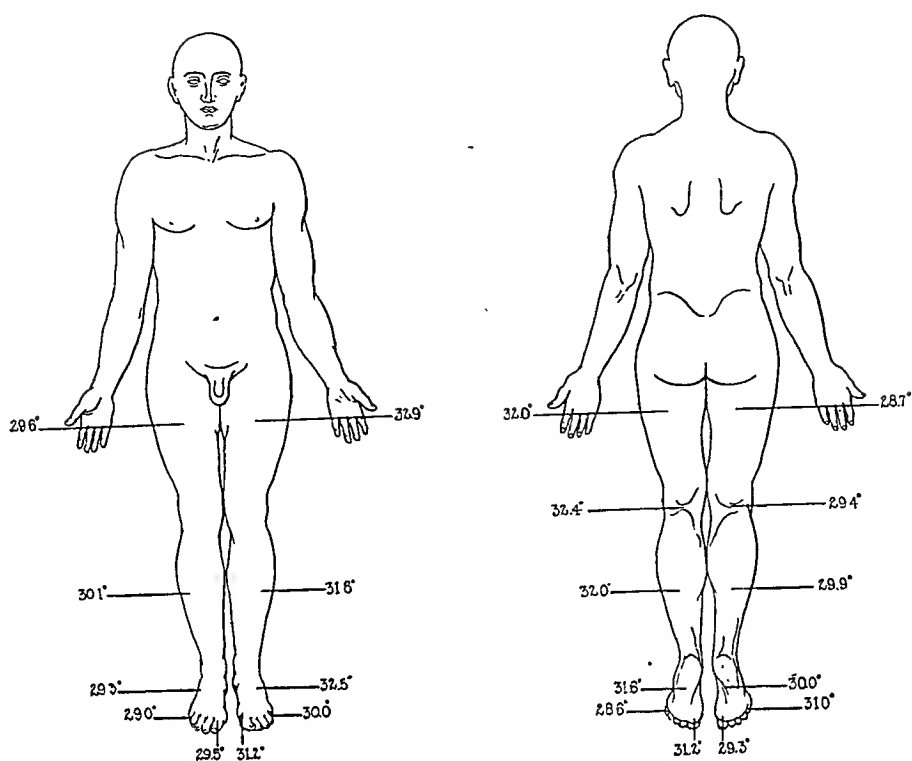


Fig. 13.—Case 9, thromboangiitis obliterans, twelfth postoperative day.

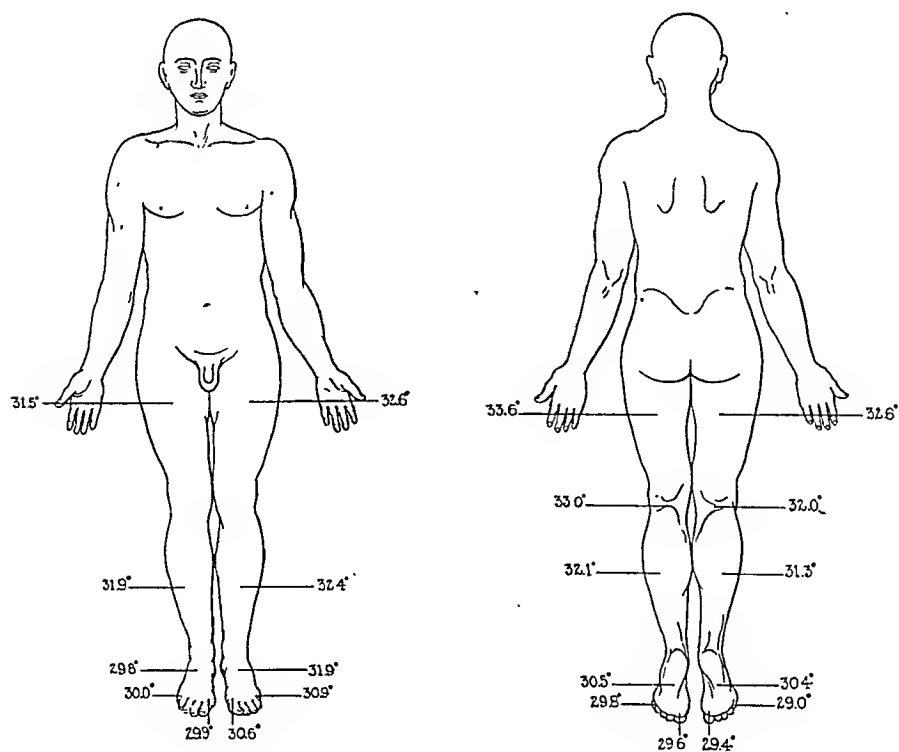


Fig. 14.—Case 9, thromboangiitis obliterans, twentieth postoperative day.

in temperature of 0.5 to 1.0 degree. (Fig. 11.) On the seventh post-operative day this effect on the right left was not observed, and the left leg was definitely warmer than the right. (Fig. 12.) On the twelfth postoperative day the left leg was still definitely warmer than the right, but its temperature was lower than at the time of the previous determination. During this period the local lesion on the great toe had undergone considerable improvement. (Fig. 13.) On the twentieth day the left leg was cooler than the right, but the left foot maintained a higher temperature than the right. (Fig. 14.)

Three features of this study deserve especial attention. The increased temperature in what is presumably the more diseased leg coincident with the development of infection indicated reflex sympathetic vasodilatation. Sympathectomy is evidently accompanied by a transient effect upon the opposite extremity. Finally the falling temperature of the left leg suggests that the effects of sympathectomy are to be only transient and that in refusing operation the patient lost his opportunity to have an amputation before his circulation regressed to its former level.

DISCUSSION

Our previous attempt to establish normal skin temperature averages for a large number of definite points over the body and extremities by studies on fifty normal medical students by the use of the dermaterm (Tycos) resulted in the determination of an average value of 32.5° for the body with a reduction of 1 to 2 degrees for the upper extremities and 2 to 3 degrees for the lower extremities. The vasomotor gradient is most pronounced in the hands and below the knees. The range of temperature variation of 4 to 5 degrees over the body, 4 to 6 degrees over the hands, and 6 to 8 degrees over the feet suggests that no accurate average standard can be set up according to which all patients should be arbitrarily judged. Comparative studies on the same patient to determine the vasomotor gradient, occlusion index, etc., by the use of various means of temporarily or permanently paralyzing the sympathetic supply to the peripheral vessels should prove of great value in estimating the relative part played by vaso-occlusion and vasospasm in the individual case of peripheral vascular disease. It can be stated that in general there is no skin temperature picture which can be considered diagnostic of any given peripheral vascular disease. The principal value of the dermaterm studies is prognostic rather than diagnostic, and the method will be found mainly useful in establishing criteria for the various types of protein shock therapy and the operative procedures upon the sympathetic nervous system which have been attempted for the relief of peripheral vascular disease.

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UNUSUAL DILATATION OF THE LEFT AURICLE*

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DILATATION of one or both auricles to a moderate degree is a common finding in chronic rheumatic carditis, but extreme dilatation of the left auricle is considered rare. The effects of the enlargement of the left auricle on the structures of the mediastinum have been known for a long time and have been repeatedly demonstrated. Among the various complications that may arise, compression of the left bronchus, paralysis of the left recurrent laryngeal nerve, and compression and displacement of the esophagus are the best known.

Many clinicians and roentgenologists, however, are skeptical of the possibility that the left auricle may dilate in a horizontal manner and form a part of the right cardiac border; yet the literature contains a number of such cases. I. Owen and W. J. Fenton¹ in 1901 first described the clinical and pathological features of such extreme enlargement of the left auricle to the right. Since then, other cases have been reported (notably^{2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14}). Bordet¹⁵ found the left auricle to the right, beyond the right auricle, in 5 per cent of a large series of cases of mitral stenosis examined by roentgenological methods.

During the past year we have had the opportunity of studying five cases of rheumatic carditis in which dilatation of the left auricle was a prominent feature. The findings in these cases resemble so closely all the reported features of extreme left auricular enlargement that we have deemed them worthy of presentation. In three of these (Figs. 2, 4 and 7), the dilatation was so extreme that the left auricle formed a large part of the right cardiac shadow, while in two others (Figs. 1 and 6), although it did not reach the same degree of dilatation, it produced pressure phenomena sufficient to obstruct the esophagus and caused an erroneous diagnosis of esophageal neoplasm to be made. One of the latter cases is especially interesting and instructive, since in overlooking the possibility of mitral stenosis with left auricular dilatation a gastrostomy was performed in another institution to relieve what was believed to be an inoperable neoplasm.

From this standpoint the lesion described here appears to be more than a mere pathological curiosity, since it serves to illustrate certain dynamic principles which should have a wider appreciation in their relation to cardiac pathology.

The following five cases will serve to exemplify the unusual and severe form of this condition.

*From the Divisions of Cardiology and Roentgenology, Philadelphia General Hospital.

CASE REPORTS

CASE 1.—B. W. A female of fifty years entered the Philadelphia General Hospital in October, 1930, complaining of dyspnea, palpitation, vomiting and inability to swallow solid food. The past history was unimportant except for the occurrence of rheumatic fever at the age of thirteen years. Her present illness started two years ago with dyspnea and at times slight edema of the ankles. For the past two months increasing difficulty in swallowing food had forced her to enter another hospital, where, after an esophageal examination, a diagnosis of malignancy was made, and a gastrostomy performed. She was transferred for radium treatment to this institution where she died on November 20, 1930, of progressive cardiac failure. *Examination:* A female of slender build, emaciated, dyspneic, with slight jaundice and cyanosis. The pulse was completely irregular. The apex was in the sixth interspace in the anterior axillary line but no thrill was felt. No murmurs were heard. The breath sounds were diminished at both bases but no moisture was



Fig. 1.

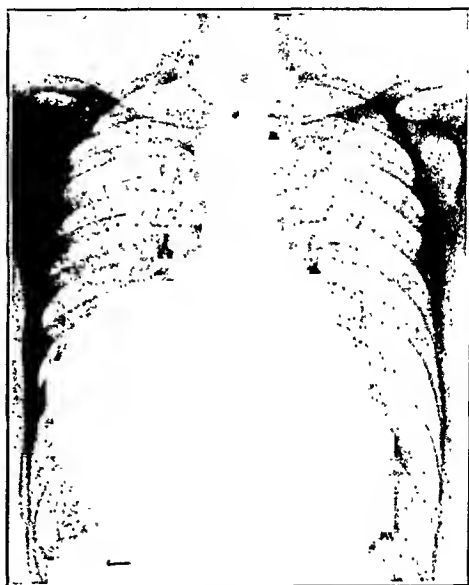


Fig. 2.

Fig. 1.—Case 1. Left oblique view showing obstruction in the esophagus at about the level of the fourth thoracic vertebra, due to large left auricle compressing the esophagus against the spine.

Fig. 2.—Case 2. Enlarged left auricle extending far to the right, over-riding the right auricle and forming the major portion of the right cardiac border. Note elevation of the bronchi and great density on right side due to superimposed left auricle.

present. The liver was enlarged and the spleen could be easily palpated. There was a distinct fluid wave in the abdomen. Electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was much enlarged in both directions, the upper left border being broadened, and the pulmonary artery together with the conus were unusually prominent. The angle of the bifurcation of the trachea was widened. Fluoroscopically, the pulsations on the left border of the heart were marked, with feeble pulsations on the right. In the right oblique position the retrocardiac space was entirely filled by the enlarged left auricle. There was a definite obstruction to the flow of barium in the esophagus at the level of the sixth thoracic vertebra (Fig. 1). Above the point of obstruction the esophagus was dilated, while below it the esophagus was displaced posteriorly and the barium passed in a very narrow stream. *Autopsy:* A poorly nourished white female, weighing ninety-four pounds. The abdomen contained 800 c.c. of yellow fluid, and the liver was enlarged and chronically congested. The spleen was enlarged with a greatly thickened capsule.

The lungs showed chronic pleuritic adhesions and scattered areas of consolidation. The heart weighed 390 gm. The valves were all normal except the mitral, which was thickened and contracted, so that it was represented by a mere slit. The auricles were both distended, but the left was twice the size of the right with a thickened endocardium and a thin, transparent epicardium. No adhesions were present. At the junction of the middle and lower third the esophagus was flattened and compressed; the depression made by the left auricle which compressed it against the spine was easily seen. The esophagus showed no evidence of any gross lesion.

CASE 2.—A. W. A male of thirty-three years entered the Philadelphia General Hospital on February 10, 1931, complaining of recurring colds, weakness, cough and loss of weight. He had had a severe rheumatic fever at the age of nine years and was well thereafter except for frequent sore throats until February, 1931, when following tonsillectomy he noticed some palpitation. *Examination:* Except for an appearance of chronic illness he seemed quite comfortable. The important findings



Fig. 3.



Fig. 4.

Fig. 3.—Case 2. Lateral view showing left auricle extending backward and right ventricle in contact with sternum in front.

Fig. 4.—Case 3. Marked dilatation of the left auricle extending to the right and forming the major portion of the right cardiac border. Left ventricle enlarged and a prominent conus on the upper left border.

in his chest were a diminished expansion at the right base with an impaired percussion note over an area corresponding to the right middle lobe in the axilla. Over this area the breath sounds were faint. The heart was enormously enlarged with the apex in the sixth interspace at the anterior axillary line. To the right of the sternum there was dullness in the third and fourth interspaces extending an inch and a half and merging with the liver dullness at the midaxillary line. A diastolic thrill was felt inside the nipple on the left and as far as the midsternum toward the right. A loud systolic murmur was heard all over the precordia, maximum at the apex and heard well to the right of the sternum. A short diastolic murmur was heard inside the left nipple. The pulse was completely irregular. There was no evidence of congestive heart failure. The electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was greatly enlarged but markedly so to the right (Fig. 2). The conus of the right ventricle was very prominent. The shadow to the right showed no pulsations and was denser than that on the left side.

The less dense right auricle could be seen to the inner side of the right border of the heart. The tracheal bifurcation was widened. In the right oblique the retrocardiac space was entirely obliterated by the left auricle and the barium filled esophagus was displaced posteriorly and to the right (Fig. 3). *Further History:* Marked improvement followed rest and digitalis therapy. He was discharged in March and returned to his clerical duties. He has continued to work and comes under occasional observation with only slight evidence of breathlessness. *Diagnosis:* Rheumatic heart disease; mitral stenosis; extreme dilatation of left auricle; auricular fibrillation.

CASE 3.—J. B. A young male of nineteen years entered Philadelphia General Hospital in June, 1930, complaining of dull aching pain over his heart and in the right chest anteriorly. At the age of ten he was ill with a severe attack of rheumatic fever, and this was followed by several minor attacks. For the past year he has had epigastric pain radiating to the right shoulder with cough and dyspnea on

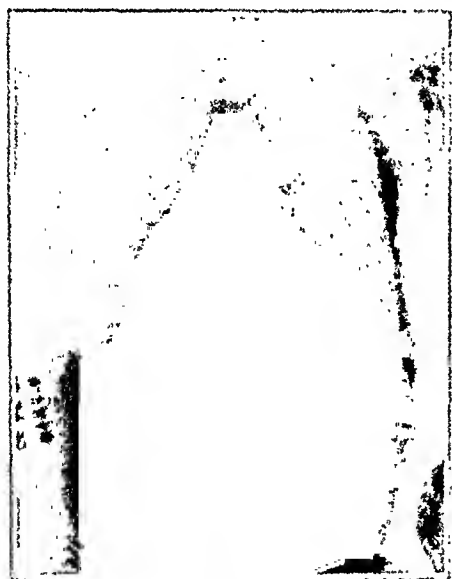


FIG. 5.



FIG. 6.

FIG. 5.—Case 4. Left ventricular hypertrophy with moderate extension of the left auricle to the right which is causing pressure on the esophagus posteriorly.

FIG. 6.—Case 4. Impression of the left auricle on the esophagus with obstruction at its lower portion.

exertion. *Examination:* He was a well-developed young man not acutely ill. His heart was greatly enlarged to both the right and the left, the apex being in the sixth interspace 3 cm. outside the nipple. There was definite impairment to percussion to the right of the sternum in the second, third and fourth interspaces. There was a slight but definite bulging in the third and fourth right interspaces in the axilla with a palpable pulsation. A diastolic thrill was felt inside the nipple. A rough systolic murmur was heard all over the precordia and to the right of the sternum. A short, rough diastolic murmur was localized inside the nipple. The pulse was completely irregular. The liver was barely palpable but no other signs of congestive failure were present. The right lower chest showed markedly diminished expansion with faint breath sounds. Electrocardiogram showed auricular fibrillation. *Bronchoscopic Examination:* The right main stem bronchus was almost completely closed below the bifurcation, due evidently to extrinsic pressure. *X-ray Examination:* The heart showed remarkable enlargement (Fig. 4). There was marked density over the right side of the heart compared with the left, and the

less dense right auricle could be seen to the inner side of the more dense left auricle. There was marked pulsation on the left border of the heart but none on the right. In the right oblique the retrocardiac space was obliterated by the left auricle. Barium in the esophagus showed marked delay at the lower third which was displaced to the right. The tracheal bifurcation was widened, and the pulmonary artery as well as the conus of the right ventricle was prominent. *Subsequent Course:* Under rest and digitalis the pain and cough improved. It was thought by some observers at this time that he had a mediastinal tumor, and he received a prolonged series of x-ray treatments with no obvious change in the size of the chest mass. He has continued to be ambulatory and his fibrillation is easily controlled. *Diagnosis:* Rheumatic heart disease; mitral stenosis; extreme dilatation of left auricle; auricular fibrillation.

CASE 4.—C. H. A male of forty-seven years entered Philadelphia General Hospital in February, 1931, complaining of cough, shortness of breath and difficulty with

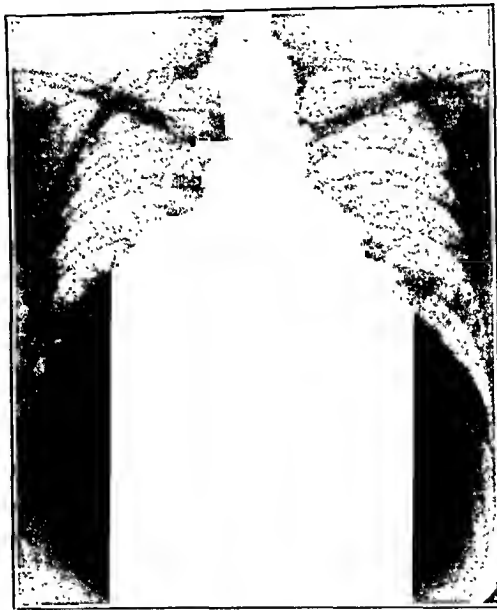


Fig. 7.—Case 5. Left ventricular hypertrophy. Left auricle extending far to the right and forming the major portion of the right border of the heart. Note prominence of conus on the upper left border of the heart.

swallowing. He denied all previous illness, having been well up to five months before admission. *Examination:* There was no evidence of dyspnea or cyanosis while the patient was lying comfortably in bed. The pulse was completely irregular. There was slight bulging of the precordia with a diffuse palpable impulse. Broadbent's sign was present. The apex was in the sixth intercostal space at the anterior axillary line, and dullness was present to the right of the sternum in the second and third intercostal spaces. There were a rough systolic apical murmur and a definite low-pitched rumble in diastole. A rough systolic murmur was heard at the aortic area. At the right base posteriorly there was relative dullness, diminished breath sounds but no moisture. Electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was greatly enlarged in its transverse diameter (Fig. 5). In the right oblique position there was definite encroachment on the midportion of the retrocardiac space. There was a definite impression in the lower portion of the esophagus, and the barium was partially obstructed (Fig. 6). There was considerable dilatation above the obstruction, and the esophagus was displaced

posteriorly. *Subsequent Course:* Under rest and digitalis he improved, but due to definite delay to the barium in the esophagus, which amounted to almost complete obstruction at its middle third, he was sent to the Radium Clinic for treatment of a possible malignancy of the esophagus. His condition remained unchanged, although under proper digitalization he was able to eat with less difficulty. He continues to be ambulatory but with definite restriction of his activity. *Diagnosis:* Rheumatic heart disease; mitral stenosis; enlarged left auricle causing esophageal obstruction.

CASE 5.—C. M. A male aged thirty-three years entered the Philadelphia General Hospital in February, 1932, complaining of pain in the right chest, cough, breathlessness and moderate weakness. At the age of eighteen he had a severe pleurisy, followed by frequent colds but no rheumatic fever. *Examination:* Well-developed white male who showed no evidence of congestive heart failure. The heart was markedly enlarged to both the right and the left. The apex was palpable in the fifth space at the anterior axilla, with a diffuse impulse in the third and fourth interspaces to the left. Dullness extended to the right of the sternum beyond the nipple line in the fourth interspace. There was a definite palpable systolic pulsation in the right axilla in the fourth interspace. There was no thrill but at the apex the first sound was sharp and had a presystolic accentuation, followed by a short systolic murmur. The lungs were clear except for diminished expansion and suppressed breath sounds over the right base posteriorly. The pulse was completely irregular and the electrocardiogram showed auricular fibrillation. *X-ray Examination:* The heart was enormously enlarged, reaching nearly to both axillary borders (Fig. 7). The pulmonary artery and conus of the right ventricle were very prominent and showed marked pulsations fluoroscopically, whereas the right border showed feeble pulsations. In the right oblique view the left auricle filled the retrocardiac space, and the esophagus was displaced posteriorly and to the right. There was no obstruction to the flow of barium in the esophagus. *Subsequent Course:* Under rest and control of the ventricular rate by digitalis, his improvement was marked. He became ambulatory, was allowed up and eventually was discharged with only moderate restricted activity. *Diagnosis:* Rheumatic heart disease; mitral stenosis; extreme dilatation of the left auricle; auricular fibrillation.

DISCUSSION

Anatomy. The left auricle makes up the posterior and superior parts of the heart; it thus lies directly posterior and is at the same time the uppermost chamber of the heart. The tracheal bifurcation lies just above it and its left branch normally rests upon it. Directly behind the left auricle lies the esophagus, which is in contact with the pericardium over it for several centimeters. Since the auricle lies posteriorly, it may enlarge either to the right or to the left but more easily to the right. When the right ventricle enlarges, the heart is pushed into an abnormal position, because it cannot enlarge in a forward direction. There results an actual rotation of the entire heart to the left, and this carries the left auricle to the right, and it comes to lie somewhat transversely across the spinal column. The left auricle can attain a greater dilatation than any other chamber of the heart. The explanation for this lies in its thin walls, the absence of safety valves into the great veins as in the right auricle and because it is often being filled by both ventricles at once when there is mitral disease. In mild degrees of enlargement the auricle extends backward beneath the bifurcation of the trachea. When the

dilatation increases it fills the space beneath the arch of the aorta, which passes over and then down, behind it, and to its left. The left ventricle is in front, often enlarged and not infrequently rotated posteriorly also as a result of the right ventricular hypertrophy. The left auricle is therefore prevented from dilating to the left, since it cannot expand through the arch of the aorta. Being also against the spine behind, it enlarges to the right, forward and upward. The right auricle now lies in front of the left, slightly below it, and the right lung if free of adhesions is easily displaced toward the right axilla.

Pathology. What is the pathology underlying this remarkable dilatation? It would seem to be due not to any one factor but to a peculiar combination of lesions, which damages one portion of the myocardium far in excess of others, leaving the remaining myocardium relatively intact and capable of maintaining an efficient circulation. In nearly all reported cases, extreme dilatation of the left auricle to the right has been associated with mitral stenosis and often with some degree of adherent pericardium. In four of our cases there were present all the physical findings of a high grade of mitral stenosis. The fifth case, on physical findings, would be classed as a moderate stenosis. That the mechanical factor is not the specific influence in the dilatation is easily realized when we consider how common mitral stenosis and insufficiency are and how rarely extreme dilatation of the left auricle is seen. In order for the auricle to dilate to this extreme degree it seems necessary for the auricular myocardium to be replaced by a tissue with relatively little elasticity. This is no doubt the basis of the pathology. The brunt of the rheumatic carditis which attacks these hearts is borne by the auricle, while the ventricle remains relatively intact. The rheumatic infection acting upon the auricle over a long period of time produces a myocarditis with gradual replacement by fibrous tissue. It is well known that the rheumatic toxin has a predilection for the walls of small blood vessels; these are often occluded, and, if the process is a gradual one, fibrous tissue replaces the auricular myocardium without an intervening stage of necrosis such as occurs with sudden occlusion. If this fibrosis is local, it may lead to aneurysmal bulging, as in a case reported by Lutembacher¹²; if more diffused, it may lead to extreme dilatation. Fibrous tissue possesses only a slight degree of elasticity and when distended, tends to remain so. When the normal safeguarding action of the muscle is lost, then the heightened auricular tension is allowed full sway and the extreme degree of dilatation discussed here may result.

Many of the reported cases show pericardial adhesions to the auricular wall, but dilatation can hardly be ascribed to the mechanical traction of such adhesions. Naturally an adherent pericardium over the auricular wall would lead to underlying fibrosis but would tend more to limit dilatation than to cause it. We have been unable to find a case reported where extreme auricular dilatation has accompanied chronic pericarditis

involving an obliteration of the pericardial sac. Indurative mediastino-pericarditis is usually associated with cardiac enlargement, but this is more liable to affect the right heart than the left. We doubt whether great cardiac enlargement is ever due to adhesion alone. The most reasonable basic explanation of this peculiar dilatation is a replacement fibrosis of the auricular wall, as first suggested by Bramwell and Duguid.⁸

The left ventricle in most of the reported cases is greatly hypertrophied and in four of our cases is apparently very large. This is certainly of extreme importance, for we believe a forceful left ventricle is essential to development of this condition. It acts in two ways. Having largely escaped the rheumatic infection, it is capable of maintaining an efficient circulation and by its vigorous action causes an increase in intra-auricular tension. It is this auricular tension acting upon a fibrous and distensible auricle which brings about this peculiar picture.

That stenosis of the mitral valve is not a necessary factor in causing left auricular dilatation is shown by the case described by Boeh and Keith,¹⁰ where huge dilatation of the auricle occurred, and yet the mitral valve was not stenosed but was thickened, producing a high degree of incompetency. Emanuel² reports two hearts showing marked auricular dilatation yet the mitral orifice readily admitted three fingers. If the lesion described as replacement fibrosis is present in the auricular wall, mitral incompetency is just as capable of producing left auricular dilatation as stenosis; probably more so, since intra-auricular pressure would be higher. In fact, Peel¹⁰ has reported a case in which dilatation of the auricles, sufficient to produce pressure symptoms suggesting a mediastinal tumor, arose from a case of heart-block without valvular lesions. Here again intra-auricular tension would be greatly increased.

Physical Signs and Symptoms. These cases present the usual symptoms associated with rheumatic carditis and the physical signs diagnostic of mitral disease. Special symptoms, however, often arise. Difficulty and pain in swallowing may be marked, as in Cases 1 and 4. This difficulty in swallowing may be extreme and lead to surgical intervention. Rösler and Weiss¹⁷ reported a series of cases in which difficulty in swallowing was a prominent feature. Pain in the chest is another common symptom and may be felt in the right axilla, at the base of the right lung or under the right breast. Cough is often severe and is caused by pressure upon the tracheal bifurcation or upon the left main bronchus.

This condition may entirely escape recognition, and its early diagnosis is only made possible by radioscopic examination. When the left auricle has dilated sufficiently to bring it near the right chest wall, then the signs will be more suggestive. To the right of the sternum in three of our cases a variable area of dullness could be mapped out. This dullness may extend into the axilla or even to the base of the right lung and be interpreted as due to pleural effusion. Over this area of dullness to

the right a systolic murmur is often heard distinctly, and there may be felt in some cases a systolic thrill. These signs are obviously due to regurgitation of blood into the auricle from the powerful left ventricle. The dullness of the heart to the right may not extend completely across the front of the chest into the axilla, but the heart dullness may be separated from the dull area in the axilla by an area of lung tympany, caused by a compression of the lung anteriorly by the enlarging left auricle. Again the heart sounds and murmurs may be heard with great intensity over the back. The anatomical relations are such that when the heart comes in direct contact with the vertebral column, the sound vibrations transmitted to the bony framework of the thoracic cage may account for the extensive area over which the systolic murmur is clearly audible. Three of our cases showed a decreased expansion of the right lower lung which must be the result of both bronchial and lung compression. In all of these three cases of great auricular dilatation, fibrillation of the auricles was present, and this has been true of most reported cases. It does not, however, seem to be a factor in the dynamics of the condition. In fact it would be most surprising if the auricles did not fibrillate when we consider the underlying pathology. The walls of the auricles, converted as they are into fibrous tissue, would seem incapable of transmitting a normal auricular impulse which depends upon continuity of muscle fibers. Since it takes but a small mass of auricular muscle to provide the path of a circus movement, we should expect fibrillation in all cases. It is true that the right auricle is often distended in fibrillation, but we have never seen a case in which the right auricle caused a palpable pulsation to the right of the sternum or in the axilla. In our three cases showing the greatest left auricular distention there was no congestive heart failure present. The greatly hypertrophied left ventricle being relatively free from disease is capable of maintaining a normal cardiac output and an efficient circulation.

Exercise Tolerance. One of the most interesting features in many of these patients with auricular dilatation is the extraordinary amount of physical activity of which they are often capable. Three of our patients showing the most extreme degree of dilatation of the auricle were able to carry on a fair degree of physical activity in spite of their valvular diseases and fibrillation. The patient in Case 2, whose heart is shown in Fig. 2, is still earning his living doing clerical work. In the two cases shown in Figs. 4 and 7 the patients are able to visit the Cardiac Clinic weekly.

The capacity of the normal auricle is considered to be between two and four ounces, yet the capacity of these greatly dilated auricles may be as much as thirty or forty ounces. The result of this storage of blood apart from the actual mechanical process of distention would be to increase tremendously the intra-auricular tension. Normally the effective pressure in the auricle is considered to be 50 mm. of water. Auricular

systole in itself plays but a small part in ventricular filling, although Straub¹⁸ states that it supplies 50 per cent of the volume, while the figures of Wiggers¹⁹ are somewhat lower. The part played by auricular systole varies with the length of diastole, but we know that hearts may function fairly efficiently without auricular systole. The question of this heightened auricular tension upon ventricular output is important in explaining both the absence of congestive failure and the excellent circulation shown under these apparent handicaps. Wiggers¹⁹ has clearly demonstrated that the systolic ventricular discharge increases progressively as venous pressure increases, and this no doubt holds for these cases. Even with narrowed mitral orifices the high intra-auricular tension will enable the ventricles to become filled during diastole, and thus the heart can maintain an efficient output. Obviously each heart has a limit beyond which such effects are no longer obtained, the limit of adaptability depending upon venous return and the cardiac muscle's condition. Our observation would lead us to believe that as long as the cardiac muscle remains efficient, the increased volume of blood contained in the left auricle is accommodated by the great expansion of its walls and that no "back pressure" effects or congestive phenomena result in the pulmonary artery or right heart.

Radioscopic Diagnosis. Radiology was long ago first applied to the diagnosis of cardiac disease, but it is still too infrequently used as part of the systematic examination. Properly used it gives as much useful information as does electrocardiography. In the diagnosis of auricular enlargement, screening of the patient is essential to a correct interpretation. When the patient faces the screen, the right border of the heart shadow is generally formed entirely by the right auricle, but under pathological conditions, where hypertrophy involves both ventricles, the lower part of the border may be formed by the right ventricle. The pulsations of the right ventricle are synchronous with the left so that the shadow of the right ventricle can be distinguished from the auricle. In mitral lesions the left auricle is the first chamber to undergo hypertrophy and dilatation. As the pressure increases in the lesser circulation the right ventricle becomes enlarged. The right ventricle forming as it does the major portion of the anterior surface of the heart, being limited by the sternum anteriorly and the diaphragm inferiorly, cannot enlarge in a forward direction. As it enlarges, it rotates the whole heart and causes the conus and pulmonary artery to be pushed upward and to the left, and the left ventricle to be carried posteriorly. Due to the rotation of the heart the knob of the aorta becomes less prominent when viewed anteriorly. The left auricle which is always posterior, never forming part of the left cardiac silhouette, goes more to the right as it enlarges, because it cannot enlarge to the left and anteriorly due to the position of the left ventricle, while posteriorly the spine and aorta limit its expansion. In the right oblique position it will be seen first

encroaching on the midportion of the retrocardiac space, and later when it further enlarges it fills the midportion of this space, the upper and lower portions remaining clear. In posterior anterior views the left auricle as it goes to the right will first be seen as a denser shadow through the less dense right auricle. As it still further enlarges, it overrides the right auricle; only the lower portion of the right border of the heart is now formed by the right auricle. With further enlargement, the left auricle passes beyond the right auricle, and in the posterior anterior view the denser left auricle can be distinguished from the less dense right auricle, particularly when the Bucky diaphragm is used. That this large shadow to the right is not the right auricle is shown by the absence of signs of right auricular distention, such as jugular enlargement, pulsating liver, and centrifugal venous pulse. All of these would certainly be present were the right auricle distended to this degree. Fluoroscopically, the right side of the heart shows very little pulsation as compared with that of the left side. The pressure on the trachea which develops in this condition makes the angle between the main bronchi more obtuse than normal. The study of the barium filled esophagus and its relation to the heart, aorta, and particularly the left auricle is very interesting and helpful. Displacement of the esophagus can be readily demonstrated, being always backward and to the right in mitral disease. This should be routinely studied in such cases, since in cardiac enlargement from other causes, the left auricle is rarely involved. The normal esophagus when viewed from the front inclines slightly to the left of the midline from the neck to the fourth thoracic vertebra. Here, as the aortic arch passes on its left, the esophagus regains the midline and bears slightly to the right. Below this, it again curves to the left, and in the lower portion it crosses in front of the descending aorta, bearing to the left until it enters the diaphragm. The patient should be examined during the act of swallowing a thick barium paste; this will cling to the walls of the esophagus for several minutes and all relations can be studied. The enlarged left auricle presses the esophagus backward and to the right; the pulsations of the auricle transmitted to the barium in the esophagus are striking. When such pulsations are present, they are always systolic in time and are obviously produced by the regurgitation of blood through the mitral orifice, since the greatly dilated auricle in fibrillation is incapable of pulsation. The esophagus will curve backward along the auricular wall; there will be a delay in the passage of the barium paste at the upper level of the auricle, and in the first right oblique position the barium will be seen to trickle in a thin stream around the convex auricular border.

Parkinson and Bedford²⁰ have shown that there may be three distinct impressions upon the barium filled esophagus when viewed in the first oblique position: first, the aortic impression, or the first curve, produced by the aortic arch as it passes backward; second, the pulmonary

artery impression, or the middle curve, due to the pressure of the left bronchus, right pulmonary artery, and the main pulmonary stem; the third impression, or the lower curve, produced by the large left auricle when present. In mitral disease, the impression made by the left auricle and the pulmonary artery is very marked.

SUMMARY

Five cases showing unusual dilatation of the left auricle have been described. In two of these esophageal obstruction was produced—in one case so pronounced as to lead to gastrostomy. In three of these cases, the left auricle extended far to the right and formed a portion of the right cardiac border. Early in the disease, x-ray examination is essential for the correct diagnosis, but in later stages diagnosis may be suspected clinically from fairly suggestive physical findings. The symptoms, physical findings, pathology, and vascular dynamics of this condition are reviewed. It is practically always seen in rheumatic hearts, with mitral stenosis and auricular fibrillation. The exercise tolerance and lack of congestive failure in some of these cases are quite remarkable.

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SPONTANEOUS RUPTURE OF THE AORTA*

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SPONTANEOUS rupture of the aorta, exclusive of aneurysm, is almost never diagnosed antemortem; hence it is seldom met with in private practice or in the hospital. It is not a great rarity, however, on a busy autopsy table, where it is seen frequently enough to justify bearing such a possibility in mind at the bedside in a differential diagnosis in cases simulating coronary thrombosis, angina pectoris, and shock, and in cases of sudden death.

In the autopsy room of Erdheim's Pathological Institute at the City Hospital in Vienna, where 2500 to 3000 necropsies are performed yearly, four or five cases of ruptured aorta are seen every year. Ames and Townsend¹ and Oppenheim² state that spontaneous rupture of the aorta is met with once in five hundred autopsies. It is much more common than rupture of the heart; yet one rarely finds a detailed description of its etiology, symptomatology, and pathology in a textbook of medicine or of heart disease, or even in a textbook of pathology. At best it is mentioned and discussed in a paragraph or two. However, the literature on the subject is fairly rich, especially of single case reports found on postmortem examination, to the astonishment of the clinician. Recently the subject has been studied carefully from the etiological and pathological standpoints by Oppenheim,² Gsell,³ Erdheim,⁴ and Levinson.⁵

Boestrom,⁶ Paschikis,⁷ Oppenheim,² Letterer,⁸ Osler⁹ and many others claim that a normal aorta under certain conditions can rupture spontaneously. Just how does such a thing take place? What is the *modus operandi*? What is the mechanism of this fatal condition, and what is the sequence of events?

For some unknown reason, owing either to a sudden strain during emotional tension, or as a result of other change in the hemodynamic system, the blood pressure in the aorta rises abruptly. If the limit of the elasticity of the tube is surpassed, the wall breaks, and thereby the pressure is reduced. Now, if the force that produces the tear in the wall of the vessel is strong enough, or the resistance low enough, all three layers of the tube break. The result is instantaneous death. If, however, the force is weaker, or the resistance of the outer coats of the wall higher, the ensuing anatomical as well as symptomatic course can be divided into two stages. Anatomically, the precipitating factor of this deadly event produces a partial rupture or tear in the wall; that is, only the

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intima and media suffer a break. This break takes place in from 75 to 90 per cent of the cases at the weakest point of the aortic tube, approximately 1 to 4 cm. above the valve, as demonstrated mechanically by Oppenheim.² The break is also most commonly on the posterior wall and is transverse. Blood now enters between the layers of the media and adventitia and is propelled further by every systole of the heart and recoil of the aorta. This produces a wider and longer separation of the two layers, and this separation advances with the increase of the quantity of blood in the newly formed space. A so-called dissecting aneurysm, first described by Laennec, is thus formed. According to Aschoff¹⁰ this is not a true dissecting aneurysm, as it has no second opening into the tube. Aschoff prefers to call it an intramural hematoma. As the pressure rises in this intramural hematoma, any additional strain resulting from muscular effort, or a physiological response such as a sneeze, cough, or even a strain at defecation, may produce a secondary rupture—the second stage in this most serious event.

If this secondary rupture is brought about gradually and into the inside of the tube, that is by another opening through the media and intima, a true dissecting aneurysm is formed, which, according to Boestrom,⁶ Laves,¹¹ and Alfejev,¹² may heal. However, in about 90 per cent of the cases, the secondary rupture is to the exterior of the tube, and in 75 per cent of such instances into the pericardium, with resulting instantaneous death.

Symptomatically, at the time of the primary rupture the individual collapses or goes into shock. After recovery from collapse, he gives a history of having been seized by sudden severe pain in the chest and at a corresponding region in the back, followed by faintness or collapse. The patient appears apprehensive, dyspneic, and either cyanotic or pale, usually the latter. He complains of pain, shortness of breath, and dysphagia. On physical examination there is usually a loud prolonged systolic murmur at the aortic valve and also in the back. There may be a thrill at the aortic valve region. X-ray examination of the cardiac region may show a widened arch, ascending or descending aorta. The blood pressure is not characteristic. A diagnosis of angina pectoris, coronary thrombosis, aortic stenosis, ruptured aneurysm, or ruptured heart is usually made.

Under rigid precautions of absolute rest and immobilization it is conceivable and possible that the secondary rupture in the second stage of this event may take place on the inside of the aorta, with resulting healing. Indeed, Boestrom⁶ reports 18 healed dissecting aneurysms out of 178 cases studied; but, as already mentioned, in 90 per cent of the cases the secondary rupture is to the exterior of the vessel, that is, through the adventitia either into the mediastinum or into the pericardium; or, if the primary tear was in the abdominal aorta, into the subperitoneal

spaces. Sudden death may ensue, therefore, when the patient is apparently on the way to improvement. Such a case is here reported:

An American seaman, J. R. W., aged fifty years, single, was admitted, ambulatory, to the U. S. Marine Hospital, Ellis Island, New York, October 8, 1931, at 4 P.M. His family history was irrelevant. He had had gonorrhea several times, the last occasion being in 1921. He had rheumatism at the age of thirty-eight years, being ill for a year. He knew of no cardiac complications at that time and was free from symptoms and in "perfect health" until the day of admission to the hospital. He was a heavy drinker. His chief complaint on admission was pain in the chest and back, and weakness. On the day of onset, while walking on the street he felt suddenly as if an "electric shock" went through his body. Everything became black before his eyes, and he had to hold on to a wall to avoid falling. After a few minutes he came to himself but was dyspneic and weak. Pain in the chest and in the back began to be severe. He went to the outpatient department of the Public Health Service from which he was sent to the hospital at Ellis Island.

Physical examination on admission showed an exceptionally well developed and well nourished male of about fifty years, very uncomfortable and dyspneic and complaining of pain. He did not appear gravely ill. The physical findings were confined to the chest. The heart was moderately enlarged to percussion and there was increased supracardiac dullness. A snappy systolic thrill was felt in the second right interspace. The first sound was hardly audible and was followed by a rough, long, rumbling murmur which continued less loudly even after the second sound, which was accentuated and snappy. The murmur was heard best over the aortic valve and also in the back. There were occasional extrasystoles. The pulses were unequal in volume. There was no deficit. Blood pressure: right 155/70, left 140/85 mm. The pupils were equal; there was no tracheal tug. Tenderness along the spine from fourth to sixth thoracic vertebrae was elicited. There was slight pallor of the face. Moist râles in both bases of the lungs were heard the next day. The liver was barely palpable. There was no edema. The temperature was 99.6° to 100.8°; the pulse rate 90 to 110; respiratory rate 24 to 28. A tentative diagnosis of coronary disease with aortic stenosis on a rheumatic basis was made. The patient was given nitroglycerin and sedatives and put to bed.

The next day the pain was slightly less, but the shortness of breath was about the same. The urine was negative, and the white blood count was normal. Blood for Wassermann reaction was not taken.

X-ray films of the heart showed the following: Enlargement of the left ventricle, dilatation of the arch and descending aorta, giving the appearance of aortic valvular disease with aneurysmal dilatation of the aorta. Both lung bases showed congestion. Electrocardiogram of the three conventional leads revealed nothing more than high voltage, left axis deviation and an inverted T_a.

On October 10, the patient had less dyspnea, but his pain was getting worse. His blood pressure showed no change; temperature was 100°, pulse rate 100 to 110. Râles in both bases of the lungs persisted. Sedatives and nitroglycerin were continued.

The next day the patient felt much better. He was sitting up in bed and was discussing something with his neighboring patients when he was suddenly heard to groan and died instantly.

Autopsy showed the following: Both pleural cavities contain a slight amount of flocculent exudate. The lungs are congested and edematous and show patches of bronchopneumonic infiltration. The pericardial cavity contains 500 c.c. of clotted blood. The heart is enlarged and there is moderate hypertrophy of the left ventricle. All valves are normal. The coronary arteries are free and patent. On the posterior

aspect of the aorta 2 cm. above the middle aortic cusp is a transverse tear 3 cm. long, with clots of blood on the edges. There is another tear 1 cm. long on the adventitial and pericardial surface. This opening leads into the pericardial sac. The wall of the aorta down to the diaphragm is split between the media and adventitia; the space is filled with clotted blood. The abdominal organs show evidence of passive congestion. Macroscopically the aorta is normal in appearance, except for a few atheromatous patches in its lower thoracic portion. It is quite elastic.

Twenty-two serial sections were made of the aorta in the region of the rupture, and it was impossible to find any pathological changes such as suppurative areas, foci of necrosis, or mucoid degeneration to account for the rupture.

COMMENT

This case then showed no reason why the aorta should have sustained such an injury. This is not surprising when one reviews the literature on this subject. More than 200 cases have been reported since the middle of the eighteenth century. One learns, however, that not all investigators are agreed as to the pathological findings in such cases. Indeed there are now two schools of thought with respect to what causes spontaneous rupture of the normal aorta. One group, Gsell,³ Erdheim⁴ and Levinson,⁵ claims that a normal aorta cannot rupture, and demonstrates definite pathological changes at the point of rupture. Another larger group, Boestrom,⁶ Oppenheim,² Letterer,⁸ Osler,⁹ Pasehki,⁷ Kutsehera,¹³ Griffiths,¹⁴ and many others, repeatedly have failed to find any demonstrable changes, and they explain the rupture on a mechanical basis.

The early investigators of the nineteenth century insisted that there must be some disease in the wall of the aorta even though they could demonstrate nothing very definite; they ascribed rupture to minor changes such as superficial atheroma and hypertrophy of the left ventricle.

Up to 1800, only two cases are recorded in the literature. The first case was reported by Nichols¹⁵ in 1761. He gave a brief account of a case of sudden death due to a ruptured aorta. Nichols found no demonstrable changes in the ruptured aortic wall.

An excellent description of a case of ruptured aorta in a woman of twenty-nine years in labor was given by Lynn¹⁶ in 1789. He related the symptoms in great detail and noted the two stages described above. The primary rupture occurred during labor and manifested itself by shock and cessation of labor pains. A diagnosis of ruptured heart was made. The child was delivered with forceps but was dead. The patient, however, began to improve later, so much so that the diagnosis of ruptured heart previously made was given up on the seventh day following delivery. The second stage of the rupture took place thirteen days after delivery with sudden death. Autopsy showed that the aorta had ruptured into the pericardium. The author reported that no specific lesion was found in the wall of the aorta, but there was no doubt that there must have been some pathological change, as parts of the inner coat

showed actual inflammation. A careful study was not possible, on account of poor light and great haste to return the body to the relatives.

Rokitansky¹⁷ in 1838 gathered eight cases and studied them from an etiological and a pathological standpoint. He stated that he found no proof of definite pathology in the wall of the aorta near the rupture, yet he concluded that a normal aorta could not rupture. Perhaps there was some developmental abnormality, he suggested.

Broca,¹⁸ in 1852, reported one case of spontaneous rupture of the aorta of a man of twenty-nine years, and reviewed the pathological findings of 28 other cases. He and Rokitansky¹⁷ stressed atheroma of the aortic wall and hypertrophy of the heart as causative factors in spontaneous rupture.

Willhelm Wollner,¹⁹ in 1856, called attention to spontaneous rupture and its relation to general arterial disease. Woodward,²⁰ in 1875, studied spontaneous rupture of the aorta and came to the conclusion that rupture may occur in a normal aorta. Harrington,²¹ in 1879, reported a case and found no pathological changes.

However, up to the time of Boestrom,⁶ in 1887, the general opinion was held that a normal aorta cannot rupture, even though no one was really able to demonstrate any definite lesion at the site of the tear. Boestrom studied primarily dissecting aneurysms. This led him to the subject of ruptured aorta, as most of his dissecting aneurysms came from that source. From an exhaustive pathological study and a review of 178 collected cases he concluded that there was no demonstrable change in the wall of the ruptured vessel and, therefore, set down the rule that a normal aorta can rupture spontaneously, and that 75 per cent of the secondary ruptures take place in the pericardium. His opinion reigned supreme until the third decade of the twentieth century, when further studies were begun.

Ames and Townsend,¹ in 1897, published a case of spontaneous rupture and stated that to that date only 100 cases had been reported in all literature. They reviewed carefully 50 cases and came to the conclusion, despite Boestrom's opinion to the contrary, that an aorta can rupture only if it is diseased in one way or another. They added nothing to the indefinite pathological picture that had been described vaguely up to that time.

In the succeeding twenty years, and especially following the war, a large number of cases of spontaneous rupture of the normal aorta appeared in the literature. More than 100 cases were reported from 1900 to 1922, and many more since then.

The tide began to turn from Boestrom,⁶ in 1906, when at the Tenth Pathological Congress at Stuttgart, the speakers discussed the subject of spontaneous rupture and were of the opinion that rupture of an aorta without underlying pathology was inconceivable.

This stimulated Oppenheim,² in 1918, to do an elaborate piece of work on this subject. After an exhaustive study of many serial sections of the walls of spontaneously ruptured aortae, he affirmed Boestrom's original contention that a normal, healthy aorta can rupture without rhyme or reason. In a further laborious and very ingenious piece of work he proceeded to investigate the mechanism and hemodynamics of this process. He wanted to know how and why the aorta usually ruptures at its ascending portion or at the arch. Following the lead of Floekerman,²² in 1898, who showed that increased pressure in the left ventricle may cause rupture of the aorta, he proceeded to find the *locus minoris resistentiae* of this vessel. He took normal hearts and aortae from human bodies fresh from the autopsy table and subjected the vessel to a pressure of four atmospheres through a rubber tube inserted into the left ventricle. The aortae would invariably rupture at the ascending portion or at the beginning of the bend to form the arch where usually fatal ruptures take place. He also noticed that this portion of the tube suffered the greatest burden of stress and strain and, therefore, burst at this point when the limits of elasticity had been surpassed. He thus concluded that a sudden rise in blood pressure may tax the ascending portion of the aorta, which is the *locus minoris resistentia*, to such an extent that rupture must follow.

He also cited numerous reported cases of ruptured aortae in aviators falling from great heights, inferring that a fall from a great altitude produces a sudden and unusual rise in blood pressure which results in rupture of the aorta at the above mentioned place.

However, the aorta continued to be of interest to many pathologists and investigators. Numerous reports of various pathological processes in the walls of the aortae that did not rupture appeared in the medical journals. Thus Pappenheimer and von Glahn,²³ Maresh,²⁴ Chiari,²⁵ Eberhardt,²⁶ Koritschoner,²⁷ and Erdheim⁴ reported a variety of pathological processes in the media and adventitia of the aorta that could easily have caused rupture of the vessel. Pappenheimer and von Glahn reported Aschoff bodies in the media in rheumatic fever cases; Maresh, Chiari, and Erdheim described foci of suppuration in the media; Cellina²⁸ and Erdheim medionecrosis and mucoid degeneration of the media.

In 1926, Gsell³ studied serial sections of eight cases of spontaneous rupture and found medionecrosis, angiomalacia, and small areas of actual suppurative inflammation in the mediae of all his cases. He advanced the theory that chronic suppurations or toxic processes in the body, such as chronic nephritis, may have a causal relationship to the processes in the wall of the aorta.

In a more recent careful study of the pathology of this subject, Levinson⁵ working in Erdheim's Pathological Institute in Vienna, reports six cases of spontaneous rupture from mild causes with microphoto-

graphic evidence of pathology in the media of every case. Levinson states that frequently the pathological process is so limited in extent and apparently so insignificant as to escape the attention of the most careful investigator unless serial sections are made extending from one extreme to the other of the tear. Such careful study necessitates as many as 50 to 65 sections. He finds that foci of suppurative inflammation, focal necroses, or mucoid degeneration of the media were present at some point along the tear in all cases studied. The tear is always larger than the pathological process. No definite organism was isolated.

Inasmuch as many investigators mentioned above have found more extensive pathological change in aortic walls of nonruptured cases, it is difficult to assume that an admittedly slight inflammatory condition or mucoid degeneration should be the whole story of the cause of spontaneous rupture.

Only one contribution was made with respect to symptomatology and physical signs as an aid in diagnosis, and that is by Conto.²⁹ He stresses sudden pain, cyanosis, a systolic thrill at the aorta and pulmonary valve, and a systolic murmur at that area as pathognomonic of rupture. In his cases, however, the ruptures took place into the pulmonary artery.

SUMMARY

A case is reported of spontaneous rupture of the aorta into the pericardium in which careful histological examination failed to reveal contributory pathological changes. Instances of such spontaneous rupture are not extremely rare, but the condition is practically never recognized during life. A review of the literature shows that such ruptures occur twice as frequently in males as in females; that age seems not be an important factor; that in many instances no changes have been found in the aortic wall and that most of such tears take place in the ascending aorta and are transverse. Usually the rupture involves at first only the intima and the media; the latter is then separated from the adventitia by a dissecting hematoma which ultimately ruptures through the adventitia at some distance from the point of the primary tear. Frequently the external rupture takes place into the pericardial sac. The symptoms and signs are discussed.

After this paper had been submitted for publication, an important article on "Spontaneous Rupture of the Aorta" by Klotz and Simpson³¹ appeared, in which the pathological findings of five cases are carefully studied. The authors report noninflammatory degeneration of the media and elastic fibers in all their five cases.

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VARIATIONS IN POTENCY OF CERTAIN COMMERCIAL PREPARATIONS OF DIGITALIS*

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A STUDY was planned requiring the use of a soluble preparation of digitalis which could be administered by intramuscular or hypodermic injection. It seemed desirable, at the start, to determine, by the technic of biologic assay, the potency of certain available commercial products. The cat method of Hatcher and Brody¹ was employed. The results of these preliminary determinations were not in agreement with the advertised claims of the manufacturers, and the variations in potency of two preparations, as well as of different lots of the same product, were astonishingly great. The investigation was therefore extended to include all of the liquid preparations of digitalis, dispensed in ampules, which are listed in *New and Non-Official Remedies*, 1931 edition. For comparison, one British product and two specimens of commercial digitalis tincture were also tested. In view of the wide use which is made of digitalis dispensed in ampules and because of the dependence of the medical profession upon these products in times of emergency, the results of our observations are here made known.

THE STANDARDIZATION OF DIGITALIS

It is only in recent years that standardization of commercial digitalis, in this country, has become common practice. In the absence of a satisfactory chemical method of assay, the biologic technic has been employed, and, for practical purposes, has been found adequate. In short, a preparation found to be potent by biologic test proves, with rare exceptions, to be therapeutically effective.

The Pharmacopeia of the United States has made official in this country the one-hour frog method. But there are products on the market, which, according to their labels, have been assayed by the guinea pig technic or the cat method; and more recently potency has been expressed by one firm in terms of the international unit. Such lack of uniformity in standardization is confusing to the clinician, since the same amounts of preparations assayed by different methods have not the same therapeutic efficacy, and the practitioner of medicine can hardly be held responsible for translating the value of one unit into terms of another. Clearly, it is desirable that there should be agreement in this matter. There are many who are of the opinion that the cat method of Hatcher is at present the best available with respect to simplicity, accuracy and cheapness.

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The American Heart Association, through its Digitalis Committee, has expressed its approval of this method by distributing to its constituent cardiac clinics throughout the United States powdered digitalis leaf assayed by the cat technic and dispensed in tablets containing one cat unit. It is of significance also that the digitalis powder which, according to a decision reached at the Geneva Conference in 1925, shall serve as the international standard, was assayed by the Hatcher cat method, slightly modified by Magnus.²

It is now usual for the drug manufacturers to advertise the fact that their digitalis products have been standardized. A mere statement to this effect, however, is not sufficient; and it is essential, if accurate dosage is to be employed, that the results of assay be expressed in units applicable to the particular preparation described.³ Some of the statements made in the advertising literature follow:⁴

(1) "Digifoline (Ciba) is of such potency that each cubic centimeter of the contents of the ampules is equivalent to $1\frac{1}{2}$ grains (approximately 0.1 gram) of digitalis leaf standardized by the Foeke method." "You may confidently choose each or all forms of Digifoline, Ciba, Doctor, with the knowledge that it is a *dependable* digitalis product."

(2) "Digitan (Merck)—a digitalis preparation of dependable potency, stable in composition, accurately assayed and physiologically standardized." "The liquid forms are equivalent, drop for drop, to a fully potent U. S. P. tincture of digitalis. One c.c. (16 minims) of these liquid forms is equivalent to $1\frac{1}{2}$ grains of potent, dried digitalis leaves."

(3) With regard to Digalen, two different types of advertising must be quoted in fairness to the Hoffmann-LaRoche Co. In the summer of 1931, when this work was begun, the claims were as follows: "Digalen (Roche) can be depended upon to give prompt action whenever the heart can respond to digitalis." No specific mention was made of standardization and the circulars suggested that "the doctor give enough for effect and in amounts adjusted to *individual case requirement*." More recently, this company has changed its policy with regard to digitalis. It is at present stated that: "The strength of Digalen in all forms is now declared in terms of cat unit potency." "We have selected the cat unit because of the increasing preference for it expressed by many cardiologists." "One ampule, 2 c.c. = 1 cat unit (cir. 150 frog units)."

(4) "Digitos (Mulford) is standardized by the lethal dose method on guinea pigs. The fatal dose for a 250 gram guinea pig is contained in one c.c." "All lots are fully and equally active." "The dosage of Digitos is the same as that of a standard tincture of digitalis."

(5) "Digitalin (Cryst.) (Burroughs Wellcome) 0.0001 gm. (gr. $1/640$ approx.) in one c.c. (Alcohol 13.5 per cent). A sterilized solution specially prepared for hypodermic injection." "Made in England by the Wellcome Foundation Ltd. for Burroughs Wellcome and Co (U. S. A.) Inc."

(6) "Tincture Digitalis (Squibb) U. S. P. X. Fat free, Physiologically tested." This means that it has been assayed by the official frog method.

(7) "Tincture Digitalis (Lederle) is not official U. S. P. strength." "It is standardized by the cat method of Hatcher, as modified and approved by the International Conference on the Standardization of Biological Products. Its potency is

*These quotations are taken from advertisements appearing in current medical journals and from circulars supplied by the manufacturing drug companies.

adjusted to a content of 1.5 cat units per cubic centimeter (15 minims).'' ''It is somewhat stronger than U. S. P. Tincture.'' ''It has dependable and uniform activity.''

To what extent claims for dependability, uniformity and potency are justified, is apparent from a perusal of Tables I and II.

ANALYSIS OF RESULTS

A. Ampule Products. It is obviously difficult to compare in a just manner a series of products prepared in various ways and assayed by different methods. For purposes of discussion, 100 per cent potency has been assumed when the cat unit was equivalent to one cubic centimeter of the liquid under examination. This assumption is entirely arbitrary, but is based on the fact that one c.c. (15 minims) of U. S. P. tincture, which is the commonly employed clinical unit of dosage in this country, contains approximately one cat unit. Three facts are immediately apparent: (1) with two exceptions to be discussed further, all lots of the various commercial preparations were below the expected potency, as estimated according to the claims in their advertising literature; (2) there was a wide range of activity in preparations manufactured by the various commercial houses; (3) in four instances, different lots of the same product were not of uniform potency, in terms of cat units.

Thus, the percentage potency of Digifoline ranged, in different lots, from 23 to 46; Digalen from 41 to 72; Digitalin from 18 to 19; and Digitos from 15 to 45. One lot of Digitan was 97 per cent of the estimated standard strength; another lot assayed only 68 per cent, according to the same estimated standard.

The Burroughs Wellcome product merits a word of special comment. It is labeled ''Digitalin (Cryst.),'' which, according to Merck's Index,⁴ is synonymous with digitonin, a glucoside which has no physiologic action on the heart. The digitalis principle contained in these ampules is clearly the crystalline ''digitaline'' of Nativelle, subsequently called ''digitoxin'' by Schmiedeberg.* In order to administer one cat unit of this incorrectly designated preparation, it is necessary to inject more than 5 c.c. of the liquid. Assuming that 0.1 mg. of digitoxin were present in one c.c., as stated on the box, the cat unit should be 3 c.c. instead of 5 c.c., since the cat unit value of the crystalline substance is 0.3 mg.¹ Even in terms of the manufacturer's standards, the contents of the ampules are only 60 per cent potent.

Specimens of Digalen, in ampules, purchased in 1931, ranged in potency from 41 to 72 per cent of the standard. The newest preparation, said to be standardized by the cat method, was 171 per cent of its actual labeled potency, in terms of cat units. From the Medical Director of Hoffmann-

*A letter from Burroughs Wellcome and Co., in reply to an inquiry concerning Digitalin (Cryst.) states that ''this substance is official in the French Codex and corresponds to the German Digitoxin.'' ''In cases of asystole amenable to digitalis an injection is made for four consecutive days. In milder cases of hyposystole, on two consecutive days, one c.c. being the injection in each case.''

TABLE I

BIOLOGIC STANDARDIZATION OF COMMERCIAL PREPARATIONS OF DIGITALIS (IN AMPULES)
BY THE CAT METHOD OF HATCHER AND BRODY

CAT NO. *	PREPARATION	LOT NO.	CAT WEIGHT KG.	DOSE C.C.	INJECTION TIME†		CAT UNIT C.C.	% OF POTENCY COMPARED TO U. S. P. TINCTURE†
1	Digifoline (Ciba)	0683	2.90	5.0		52	1.72	58.0
2	Digifoline (Ciba)	0683	2.95	6.0	1	14	2.03	49.2
3	Digifoline (Ciba)	0683	4.18	10.0	1	25	2.38	42.0
4	Digifoline (Ciba)	0683	3.55	8.5	1	29	2.39	41.8
5	Digifoline (Ciba)	0683	3.25	7.5	1	37	2.31	43.3
6	Digifoline (Ciba)	{ 0683 07983	3.35	6.0	1	40	1.79	55.8
7	Digifoline (Ciba)	0683	4.12	10.0	2	50	2.42	41.0
Average	Digifoline (Ciba)	0683					2.15	46.5
1	Digifoline (Ciba)	07983	4.22	17.5	2		4.15	24.0
2	Digifoline (Ciba)	07983	3.58	16.5	4	20	4.61	21.8
Average	Digifoline (Ciba)	07983					4.37	22.9
1	Digitan (Merck)	30521	3.65	4.0		38	1.10	90.9
2	Digitan (Merck)	30521	4.20	3.4		58	.81	123.5
3	Digitan (Merck)	30521	4.00	4.0	1	09	1.00	100.0
4	Digitan (Merck)	30521	4.10	3.6	1	24	.88	114.0
5	Digitan (Merck)	30521	3.25	3.6	1	30	1.11	90.1
6	Digitan (Merck)	30521	4.25	5.0	1	30	1.17	85.5
7	Digitan (Merck)	30521	3.45	4.0	1	49	1.16	86.0
Average	Digitan (Merck)	30521					1.03	97.0
1	Digitan (Merck)	32840	3.22	4.0	1	11	1.24	80.0
2	Digitan (Merck)	32840	3.02	4.0	1	12	1.33	75.0
3	Digitan (Merck)	32840	3.85	6.0	1	37	1.56	64.2
4	Digitan (Merck)	32840	2.95	5.0	1	40	1.70	59.0
Average	Digitan (Merck)	32840					1.46	68.5
1	Digalen (Roche)§	204169	2.95	7.0	1	32	2.37	42.1
2	Digalen (Roche)§	204169	2.75	6.5	1	39	2.36	42.3
3	Digalen (Roche)§	204169	3.50	8.0	2		2.29	43.8
4	Digalen (Roche)§	204169	3.45	9.0	2	12	2.61	38.3
Average	Digalen (Roche)§	204169					2.41	41.6
1	Digalen (Roche)§	311030	3.43	5.0	1	25	1.46	68.6
1	Digalen (Roche)§	311130	3.62	5.0	1	17	1.38	72.4
1	Digalen (Roche)	311191	2.90	3.6		48	1.17	171.0
2	Digalen (Roche)	311191	3.55	3.7	1	02	1.05	190.4
3	Digalen (Roche)	311191	3.75	4.5	1	17	1.23	162.8
4	Digalen (Roche)	311191	4.10	4.5	1	28	1.10	182.0
5	Digalen (Roche)	311191	2.75	3.5	1	30	1.28	156.2
Average	Digalen (Roche)	311191					1.17	170.9
1	Digitalin (Burroughs-Wellcome)	15004	3.05	15.0		57	4.92	20.3
2	Digitalin (Burroughs-Wellcome)	15004	4.40	23.0		59	5.23	19.1
3	Digitalin (Burroughs-Wellcome)	15004	3.70	19.5	1	02	5.27	19.0
4	Digitalin (Burroughs-Wellcome)	15004	4.10	21.5	1	08	5.24	19.0
5	Digitalin (Burroughs-Wellcome)	15004	3.22	21.0	2	44	6.52	15.3
Average	Digitalin (Burroughs-Wellcome)	15004					5.44	18.5

TABLE I (CONTINUED)

CAT NO.*	PREPARATION	LOT NO.	CAT WEIGHT KG.	DOSE C.C.	INJECTION TIME		CAT UNIT C.C.	% OF POTENCY COMPARED TO U. S. P. TINCTURE†
1	Digitalin (Burroughs-Wellcome)	32513	2.5	12.0	1	24	4.80	20.4
2	Digitalin (Burroughs-Wellcome)	32513	3.1	16.5	1	32	5.32	18.8
Average	Digitalin (Burroughs-Wellcome)	32513					5.06	19.6
1‡	Digitos (Mulford)	700965A	2.45	4.0		43	1.63	61.3
2	Digitos (Mulford)	700965A	3.17	6.5	1	10	2.05	48.8
3	Digitos (Mulford)	700965A	3.13	6.5	1	21	2.09	48.2
4	Digitos (Mulford)	700965A	3.03	9.0	2	18	2.97	33.7
Average	Digitos (Mulford)	700965A					2.19	45.6
1	Digitos (Mulford)	675482A	3.4	9.0	1	23	2.65	37.8
1	Digitos (Mulford)	675482A	3.2	20.7	2	22	6.47	15.5
		659933A						

*Adult male cats used.

†One hundred per cent potency is assumed when one c.c. contains one cat unit. This assumption is arbitrary, and is based on the fact that one c.c. of U. S. P. tincture contains approximately one cat unit.

‡Not fully grown.

§Obtained in 1931. No reference to standardization.

||Obtained in 1932. Said to be standardized by the cat method and put up so that 2 c.c. equal one cat unit.

¶It has been shown that the injections may be made over periods varying from ten minutes to three or four hours, and the duration of the experiment, within these limits, exerts little or no effect upon the ultimate dose required. [Eggleston, C., Biological Standardization of the Digitalis Bodies by the Cat Method of Hatcher, Am. J. Pharm. 85: 99, 1913.]

LaRoche, Inc., it was learned that these standardizations were carried out in the company's laboratories in Switzerland. Herein may lie one reason for variation. It has been shown that guinea pigs reacted differently to the same brand of nearsphenamine when sensitization experiments were carried out in Breslau, Zürich and New York, in spite of care in providing for an identical technic. On the basis of these observations, Sulzberger and Mayer⁵ point out that diet as well as other influences, such as nonhomogeneous races of laboratory animals, must be taken into account in the interpretation of experimental results in different localities. Furthermore, in the standardization of digitalis, Macht⁶ found that biologic assays by the cat method varied with altitude and the state of the weather.

Quite recently, assays of various commercial preparations of digitalis have been carried out in Germany in a manner comparable to our own.⁷ In the pharmacological laboratories of the Universities of Heidelberg, Leipzig, and Giessen, biologic assays of ampule products, liquid digitalis and tablets were made by the Straub-Houghton frog method. The figures obtained with the same products in the three laboratories were in close agreement. All of the preparations examined contained digitalis in amounts below the values ascribed to them by the manufacturers. For example, the liquid in an ampule of Digalen was 48 per cent of its supposed strength; Digifoline was 25 per cent potent; and Digipurat, which

TABLE II
BIOLOGIC STANDARDIZATION OF COMMERCIAL TINCTURES OF DIGITALIS BY THE CAT
METHOD OF HATCHER AND BRODY

CAT NO.*	PREPARATION	LOT NO.	CAT WEIGHT KG.	DOSE C.C.	INJECTION TIME HR. MIN.	CAT UNIT C.C.	% OF POTEN- CY COMPARED TO U. S. P. TINCTURE†
1	Tincture Digitalis (Squibb)‡	OK2384	3.53	3.0	51	0.849	117.7
2	Tincture Digitalis (Squibb)‡	OK2384	4.30	3.75	1 15	0.872	114.7
3	Tincture Digitalis (Squibb)‡	OK2384	3.27	2.80	1 16	0.857	116.8
4	Tincture Digitalis (Squibb)‡	OK2384	2.95	2.90	1 28	0.989	101.0
5	Tincture Digitalis (Squibb)‡	OK2384	4.50	4.75	2	1.05	94.4
6	Tincture Digitalis (Squibb)‡	OK2384	3.17	3.0	2	0.946	105.7
Average	Tincture Digitalis (Squibb)‡	OK2384				0.927	108.4
1	Tincture Digitalis (Lederle)	225H23H	3.10	1.50	44	0.484	137.8
2	Tincture Digitalis (Lederle)	225H23H	2.78	1.50	54	0.539	123.8
3	Tincture Digitalis (Lederle)	225H23H	3.10	1.40	1 19	0.453	147.2
4	Tincture Digitalis (Lederle)	225H23H	3.70	2.25	1 25	0.608	109.7
5	Tincture Digitalis (Lederle)	225H23H	4.70	2.50	1 30	0.532	125.4
6	Tincture Digitalis (Lederle)	225H23H	3.95	2.13	1 30	0.538	124.0
Average	Tincture Digitalis (Lederle)	225H23H				0.526	128.0

*Adult male cats used.

†One hundred per cent potency is assumed when one c.c. contains one cat unit. This assumption is arbitrary, and is based on the fact that one c.c. of U. S. P. tincture contains approximately one cat unit.

‡"Tincture Digitalis, U. S. P. X. Fat free. Physiologically tested." E. R. Squibb & Sons.

||"Tincture Digitalis Lederle, standardized May 12, 1930, obtained from Lederle Antitoxin Laboratories on June 8, 1931. "Fat free. Physiologically standardized by the cat method of Hatcher. One c.c. contains 1½ cat units." The cat unit, in this instance, should be 0.667 c.c. The per cent of estimated potency has been calculated on this basis.

is the German preparation of Digitan, was 92 per cent of its estimated potency. These figures for the ampule products approximate some of the assay values which we have obtained for preparations of the same name marketed in America. Different lots of the same preparation also showed wide variations in biologic activity. The German authors conclude that "the greatest variation from the average is far larger, in some preparations, than would be present in carefully prepared products."

B. *Tinctures*. The tinctures, in contradistinction to the ampule products, were fully potent. That of Squibb, standardized by the manufacturer by the one-hour frog method, yielded a value of 108 per cent; that

of Lederle, said to be standardized by the cat method, was 128 per cent of its labeled activity.

DISCUSSION

What are the possible causes for such variations in potency? Differences in the method of standardization first suggest themselves. Yet it is a fact that one cubic centimeter of a preparation properly standardized by the frog method is equivalent to one cat unit, as may be seen by referring to the results obtained with Squibb's tincture (Table II). Furthermore, variability of different lots of the same product cannot be accounted for on this basis.

It has been shown that aqueous solutions of crystalline strophanthin (Ouabain), put up and sterilized in soft glass ampules, deteriorate rapidly, due to a change in hydrogen-ion concentration toward the alkaline side, with resultant decomposition of the glucoside molecule.^{8, 9} Such deterioration can be prevented by employing hard glass ampules and using a buffer solution (phosphate mixture of P_H 7.0) as solvent.⁸

Accordingly, determinations were made of the hydrogen-ion concentration of the contents of the various ampules containing digitalis (Table III). Of the five preparations examined, three were acid in reaction, one was sharply alkaline, and the fifth (Digitan, Merck), though slightly alkaline, more nearly approached neutrality. It is noteworthy that this latter preparation was the most potent of the group.

To what extent an acid or alkaline reaction may affect the strength of aqueous solutions of digitalis, particularly after sterilization by heating in a sealed glass container, we have not attempted to determine. After a study of the relationship of P_H to the potency of digitalis infusions, Tainter¹⁰ concluded that the hydrolytic cleavage of the glucosides which goes on slowly at room temperature and the natural P_H , is accelerated by an increase in acidity or alkalinity as well as by a moderate increase in temperature. By analogy with the observations on crystalline strophanthin, it is reasonable to infer that changes in P_H may play a rôle, and that a sharply alkaline reaction particularly is to be avoided.*

In digitalis tinctures neither age, within reasonable limits, nor reaction influences materially the stability, although the effect of age on deterioration must probably be taken into account with the aqueous solutions.⁹

All of the factors necessary for a reliable product are readily controllable, and the conclusion seems inevitable that the fault lies with the

*The following note was received from Dr. Walter A. Jacobs, Member of the Rockefeller Institute for Medical Research, after he had reviewed the results of our experiments. Dr. Jacobs' work on the chemistry of the digitalis bodies has appeared over a period of years, chiefly in the *Journal of Biological Chemistry*. "I believe that there is no question that the deterioration of digitalis solutions is referable to the wide variation in P_H which has been found on examination of these solutions. We now know that the strophanthin and the digitalis bodies are very closely related substances. They possess in common certain chemical groups which make them more or less susceptible to acids or alkali. The latter produces definite chemical alterations in these substances with consequent pharmacological deterioration. I am sure that the method of using a buffer, which you found so useful in preserving solutions of ouabain, should be similarly applicable to other strophanthins as well as the digitalis glucosides and extracts."

TABLE III

HYDROGEN-ION CONCENTRATION OF COMMERCIAL PREPARATIONS OF DIGITALIS MARKETING IN GLASS AMPULES*

(Each figure given represents the average of determinations made on the contents of each of three ampules)

PREPARATION	P _H
Digifoline (Ciba)	5.4 †
Digalen (Roche)	6.4 †
Digitalin (Burroughs-Wellcome)	6.0 †
Digitos (Mulford)	8.0 †
Digitan (Merck) Lot No. 32840	7.47‡
Digitan (Merck) Lot No. 30521	7.70‡

*We are indebted to Dr. R. F. Loeb for these determinations.

†Colorimetric method.

‡Determined by quinhydrone electrode.

commercial drug houses. A pertinent example is furnished by experience with Digalen, manufactured by Hoffmann-LaRoche, Inc. This preparation was omitted from *New and Non-Official Remedies* by the Council on Pharmacy and Chemistry of the American Medical Association in 1914, because of misleading advertising claims and because of "quantitative differences in activity to the extent that some specimens examined were more than twice as active as others."¹¹ It is of interest to find that some of the figures then published by the Council, expressing the potency of various samples of Digalen (liquid) in terms of cat units (c.c. per kg.) are almost identical with those given in Table I (Lots 204169, 311030 and 311130). The 1914 figures are 1.52, 1.67, 1.73, 1.95, 2.03, 2.39, 2.50, 3.10 and 3.32. The newest Digalen liquid, in ampules (Lot 311191), standardized by the cat method by the manufacturer, showed in our laboratory a cat unit value of 71 per cent *greater* than its labeled biologic potency.

The results of our observations appear to indicate lack of adequate care on the part of the manufacturing drug firms in the preparation of digitalis products marketed in ampules. A sharp rebuke for misbranding the potency of a digitalis tablet was recently administered to one of these commercial houses.¹² A further lesson is evidently necessary. The situation calls for prompt remedial measures.*

SUMMARY

1. Different lots of five commercial preparations of digitalis, marketed in ampules, have been biologically assayed by the cat method of Hatcher and Brody.

*Our findings were communicated to the Medical Director of Hoffmann-LaRoche, Inc. In May, 1932, after this paper was submitted for publication, a letter was received from the Scientific Department of this company stating the following: (1) re-assay by the Roche Laboratories in Europe yielded a value which agreed with the original European assay; (2) the assay value of the ampule product, as determined by an American pharmacologist, as well as by the Referee on Digitalis of the Council on Pharmacy and Chemistry of the American Medical Association, agreed with that reported in this paper; (3) on the basis of these observations, the strength of Digalen solution has now been adjusted to correspond with the American assay, in terms of cat units; (4) all Digalen products sold in America will, in future, be assayed in this country.

2. Samples of all of the preparations so examined were found to be below the expected potency, as estimated in terms of a standard U. S. P. tincture. One lot of Digitan, however, was 97 per cent active. The newest preparation of Digalen, standardized by the manufacturer by the cat method, was 71 per cent stronger than its labeled biologic activity.

3. In four instances, different lots of the same product showed wide variations in potency.

4. Such variations in the strength of digitalis products marketed in ampules appear to indicate lack of adequate care on the part of the manufacturing drug firms in their preparation and labeling. The situation calls for prompt remedial measures.

5. Two specimens of commercial digitalis tincture were found to be fully potent. One sample was 28 per cent stronger than its labeled activity.

6. The one-hour frog method of digitalis assay, now official in the U. S. Pharmacopeia, has evidently not been found generally satisfactory for practical purposes, as evidenced by the continued use of cat, guinea pig and international units. It would be helpful both to the practitioners of medicine and to the drug manufacturers if a uniform standard were agreed upon and universally adopted in this country.

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MINIMAL TOXIC AND LETHAL DOSAGE OF DIGITALIS IN EXPERIMENTAL HYPER- AND HYPOTHYROIDISM*

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INTRODUCTION

THE tachycardia in clinical hyperthyroidism with or without auricular fibrillation and in the presence or absence of congestive heart failure does not usually respond to digitalis administration by slowing as well as it does in patients with a normal basal metabolic rate.¹ In view of this, experiments were planned in order to ascertain whether any difference existed in the amounts of digitalis necessary to cause toxic and lethal effects in normal, hyper- and hypothyroid rabbits.

METHOD

A modification of the Hatcher method² as used by Levine and Cunningham³ was employed. The digitalis preparations were injected intravenously, by means of a small syringe, into the marginal ear veins of rabbits. The doses were divided and given at six-minute intervals. No anesthetic was used. It has been found that both the toxic and the lethal doses of digitalis are independent of the speed of administration of the drug in cats when the experiment is conducted within a period of from fifteen minutes to four hours⁴ and that the effects from digitalis are lost more rapidly in rabbits than in cats.⁵ Experiments of comparatively short duration were therefore thought advisable. For this reason the size of the doses was adjusted so that a lethal result would be obtained in about thirty to forty minutes in each experiment. The method was checked by the use of crystallized ouabain (Arnaud) in two experiments on normal rabbits. The minimal lethal doses found in these two normal rabbits agreed closely with those obtained by Hatcher.⁶ Thereafter, a proprietary injectable tincture of digitalis (Digalen-Hoffman La Roche) was used.

TECHNIC

Electrocardiograms were taken from leads applied to the right foreleg and left hindleg of the animals. Tracings were made one minute before each injection and more often when toxic or lethal effects were being approached. After the experiment

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This study was conducted in part under a grant from the Proctor Fund for the Study of Chronic Diseases.

was completed, the first appearance of ectopic beats in the tracing was taken as the earliest indication that the toxic dose had been administered.⁴ Auscultation of the heart at frequent intervals often gave an indication that an electrocardiographic tracing should be taken between the usual six-minute intervals. The minimal lethal dose was that amount of the drug which just caused standstill of the heart and death.²

Twenty-one rabbits were used. Eight were made "hyperthyroid"; of these, six received one mg. thyroxin (Squibb) subcutaneously each day for three days, and two were fed 0.260 gm. (gr. iv) desiccated thyroid gland (Armour) daily for three weeks. In each instance the basal metabolic rate became definitely elevated and ranged from +45 per cent to +90 per cent, averaging +54.6 per cent above the normal level. Three of the animals were thyroidectomized and their basal metabolic rates determined at frequent intervals until in each case the rate fell to -30 per cent or lower. The average basal metabolic rate of this group of hypothyroid rabbits was -32.5 per cent. Ten normal rabbits were used as controls. The basal metabolic rate of these animals was determined in most cases and was always within normal limits.

The oxygen consumption was determined by means of a Benedict portable respiration apparatus⁶ connected to a water-sealed animal chamber, using an outside electric motor blower. Wilson's soda lime was used for the absorption of carbon dioxide. The animals were fasted at least eighteen hours before each test. Successive ten-minute periods of measured oxygen consumption were run until three consecutive checks were obtained.

RESULTS

There was a striking lack of difference in the cardiac response of the animals in the three groups to the action of digitalis (Table I). The average minimal toxic dose varied from 196 to 213 mg. per kg. The average minimal lethal dose was likewise almost constant, ranging in the three groups from 318 to 324 mg. per kg. The percentage of the minimal lethal dose which was toxic varied from 60.8 per cent to 65.3 per cent. This is in agreement with the observations of other workers who used only normal animals.^{3, 4, 7} It is evident that the toxic and lethal doses of digitalis were not altered by the changed metabolism of the hyper- and hypothyroid animals.

Hatcher found that the fatal dose of digitalis in normal rabbits weighing 1800 gm. or less to be from 200-250 mg. per kg.⁵ In our experiments the average minimal lethal dose in normal rabbits averaging 1940 gm. in weight was 318 mg. per kg., and the average minimal lethal dose in the three groups of animals was 320 mg. per kg. The weights of the animals in these groups averaged 2180 gm. A preliminary check of the

TABLE I

THE MINIMAL TOXIC AND MINIMAL LETHAL DOSES OF DIGITALIS IN MG. PER KG. IN NORMAL HYPER- AND HYPOTHYROID RABBITS

GROUPS	NO. ANIMALS	AV. BMR%	AV. MTD	AV. MLD	MTD
			MG/KG	MG/KG	—% MLD
Normal	10	±0	203	318	63.8
Hyperthyroid	8	+54.6	196	322	60.8
Hypothyroid	3	-32.5	213	324	65.3

method with ouabain had yielded results almost exactly similar to those obtained by Hatcher with ouabain in rabbits. The fact that our minimal lethal dose of digitalis was higher than that reported by Hatcher was due, apparently, to lower potency of the digitalis preparation which we used.

In all the rabbits except three the earliest sign of digitalis toxicity was the appearance of ectopic ventricular beats in the electrocardiogram. In two of the three exceptions premature auricular beats appeared first; in the remaining animal the first electrocardiographic abnormality to appear was a change in the character of the QRS complex. This may be considered an evidence of digitalis intoxication.⁷ The three animals mentioned above died of digitalis poisoning without showing curves typical of ventricular extrasystoles.

No constant effect on the character of the T-wave was observed in the animals.^{8, 9} There was one instance of flattening and one of inversion of the T-wave, and in another single case the T-wave became inconstant in shape after the toxic dose had been reached. These changes took place shortly before death. The T-waves remained unaffected in the remainder of the cases.

The commonest cardiac arrhythmia just prior to death was multiple ventricular ectopic beats. There were occasional instances of auricular fibrillation, auriculoventricular dissociation, paroxysmal ventricular tachycardia and ventricular fibrillation. Electrocardiographic tracings in many cases were not continued until final cardiac standstill occurred.

CONCLUSION

Hyperthyroidism was produced in eight rabbits, and hypothyroidism in three rabbits. It was found that the minimal toxic and minimal lethal doses of digitalis in these two groups were not significantly different from those in normal animals.

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OBSERVATIONS ON ELECTROCARDIOGRAPHY IN HEART DISEASE ASSOCIATED WITH PREGNANCY WITH ESPECIAL REFERENCE TO AXIS DEVIATION*

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PHYSICAL examination of the heart during the course of pregnancy not infrequently reveals signs which may suggest heart disease to the examiner. Tachycardia, systolic murmurs, usually at the base, less often at the apex, reduplicated sounds, or third heart sounds and accentuated apical first sounds are found which are sufficient to cause one out of nine pregnant women when first seen to be referred to the cardiac clinic at the Boston Lying-In Hospital for further study. These signs may or may not be accompanied by mild dyspnea on exertion, night starts, palpitation and sighing respiration, together with a doubtful or even a positive rheumatic history. Sometimes symptoms alone are grave enough to require special cardiac examination. In such cases, in addition to physical examination and x-ray study, one resorts to electrocardiography, especially for the estimation of the axis deviation as an aid in making a diagnosis or excluding the possibility of rheumatic valvular heart disease or congenital cardiac defect.

During pregnancy the special and variable condition under which the electrocardiographic examination is made results from the influence on the height of the diaphragm of the enlarging uterus or from the gradually increasing physiological load on the cardiovascular system and the organism generally. Jensen and Norgaard¹ studied the axis deviation as estimated by the relation between R_3 and S_3 in 239 normal pregnant women and found a tendency toward left axis deviation during the first months of pregnancy, and in the later months a return toward the right deviation. In their opinion this was independent of any change in position of the heart. They interpreted their findings as an early left ventricular hypertrophy followed by a later compensatory right ventricular hypertrophy. We have tabulated and averaged the axis deviation of 193 electrocardiograms on normal patients taken at various times during pregnancy and have found, as illustrated by Fig. 1, that the axis shifts to the left during the first two trimesters of pregnancy and tends to return to the right during the last trimester, the most definite shift to the right in our experience occurring between the eighth and ninth months. We suspect that this effect late in pregnancy may be due to the phenom-

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enon of "lightening" when the uterus assumes a somewhat lower position as it commonly does when the head engages during the last weeks of pregnancy in primiparae. A similar effect in multiparae results from the more pendulous abdomen late in pregnancy when the uterus and its contents fall forward with consequent release of upward pressure on the diaphragm. Not infrequently both normal women and women with organic heart disease experience amelioration of dyspnea at this time. Whether one interprets this shift in the electrical axis of the heart as

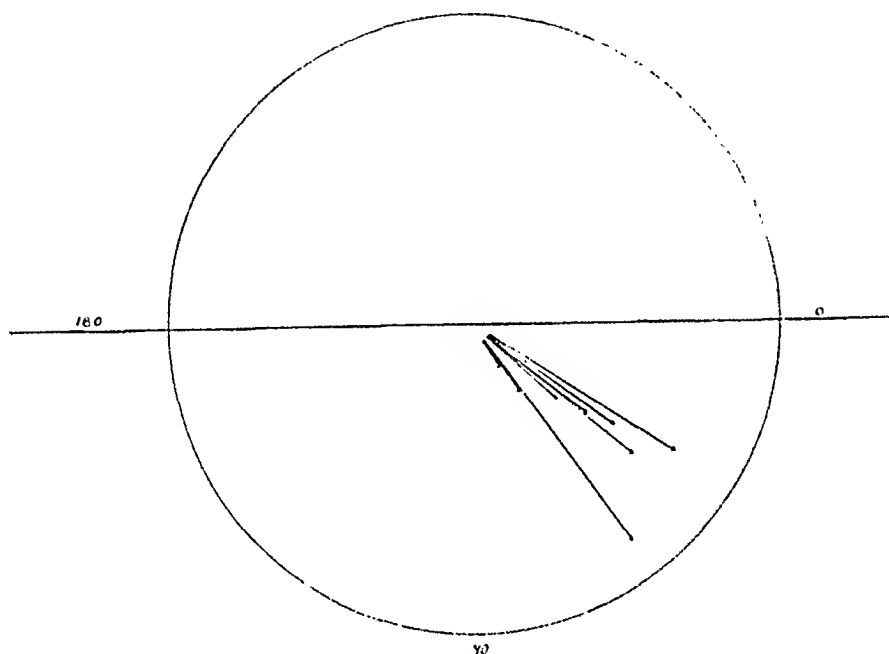


Fig. 1.—Arrows represent the average electrical axis of the heart determined from 193 electrocardiograms on normal patients at different months of pregnancy from the second through the ninth. The length of the arrow indicates the month from the shortest, second month, to the longest, ninth month. The distribution of the cases and the average angle found were as follows:

MONTH OF PREGNANCY	NO. OF ELECTROCARDIOGRAMS	AVERAGE ANGLE
2	5	56
3	15	54
4	20	40
5	38	37
6	33	35
7	41	38
8	29	32
9	12	53

It appears that the electrical axis tends to shift toward the left during the first two trimesters of pregnancy and to return toward the right during the third trimester.

first a left and then a compensatory right ventricular hypertrophy as do Jensen and Norgaard,¹ or as due to changes in position of the heart which are mechanical in nature as we are inclined to suspect, it is nevertheless clear from our findings that there is a definite progressive tendency toward left axis deviation in the electrocardiogram from the second to the sixth month, while the axis remains about the same in the seventh and eighth months, definitely shifting back to the right in the ninth month. A further shift to the right is commonly, though not always,

noted after parturition. This is shown in Fig. 2, which represents the electrical axis in four normal patients at the ninth month and after the puerperium. The shift was from twenty to thirty degrees to the right in three cases. There was no shift in the fourth case.

It is apparent from these considerations that the estimation of axis deviation probably will not be useful in the study of patients during pregnancy unless interpreted in the light of these results. This is illustrated by the electrocardiographic findings in forty-nine cases of

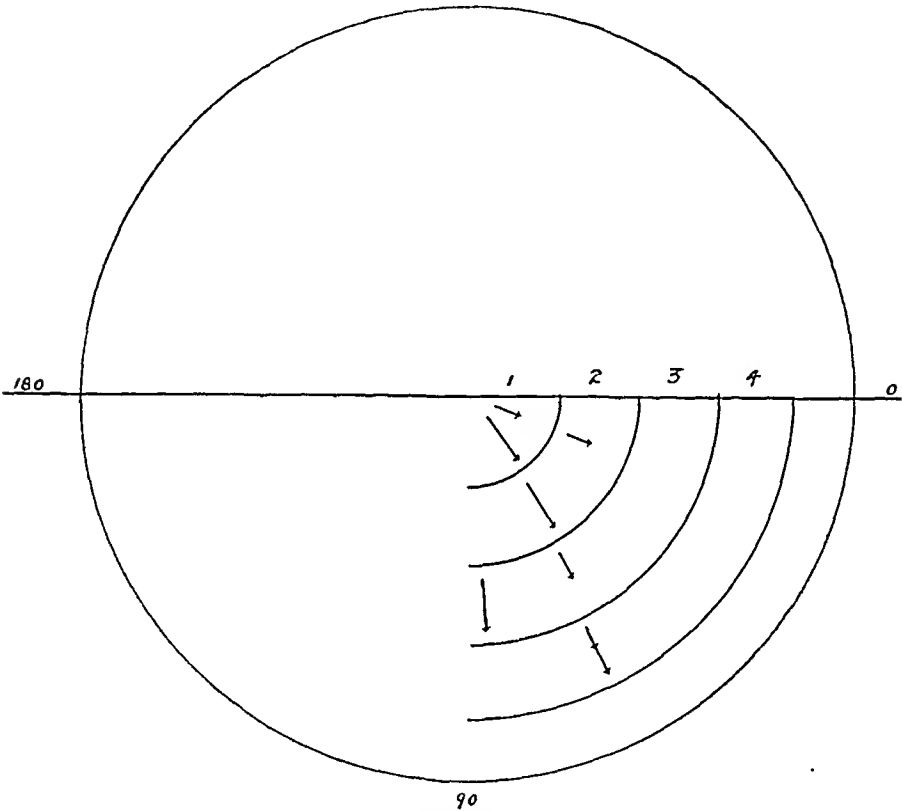


Fig. 2.—The electrical axis of the heart late in pregnancy and postpartum in four patients with normal hearts. The four patients may be summarized as follows:

PATIENT	AGE	PARITY		ELECTRICAL AXIS		ELECTRICAL AXIS
1	25	ii	9th mo.	20	6 wk. postpartum	52
2	21	i	9th mo.	20	2 wk. postpartum	56
3	27	iv	9th mo.	59	3 mo. postpartum	85
4	23	ii	9th mo.	62	2 mo. postpartum	62

The shorter arrow represents the angle at the ninth month of pregnancy and the longer arrow the angle found postpartum.

organic heart disease in pregnant women. Only thirteen showed abnormal axis deviation, considering 0 to 90° as the normal range. There were twenty-five cases of mitral stenosis of rheumatic origin. One showed right axis, three showed left axis deviation, and the remaining twenty-one were normal. There were nine cases of organic mitral regurgitation of rheumatic origin. One showed right axis deviation, four showed left axis deviation, four had normal axes. There were

twelve cases of aortic regurgitation. Nine had normal axes, three showed left axis deviation. There were three cases diagnosed as congenital heart disease. One of them showed right axis deviation. Two had normal axes. *It is apparent, therefore, that unless a sufficiently large number of normal pregnant women could be electrocardiographed each month during pregnancy so that the average shift of the heart could be accurately estimated and the Einthoven triangle rotated in the appropriate direction by an accurate average amount, the use of axis deviation as ordinarily interpreted for aid in the diagnosis of valvular disease or congenital defects during pregnancy is likely to be unsatisfactory.*

While reviewing our findings in regard to axis deviation we found twenty-nine, or slightly less than 11 per cent of 264 electrocardiograms showing complete inversion of Lead III. In about half of these cases the electrocardiogram was taken in the third trimester of pregnancy. The outcome of the pregnancy was good for both mother and baby in twenty-six of the patients on whom the electrocardiograms were taken, good for the mother while the baby was stillborn in one, and good for the mother in one case while one of twins was stillborn, and one was viable. The outcome was unknown in one patient delivered by her local doctor. Our conclusion was that this finding represented a transverse position of the heart and was not indicative of any organic change. This is in agreement with the findings of Bland and White.²

CONCLUSIONS

1. Electrocardiographic study for the estimation of axis deviation as an aid in the diagnosis of acquired valvular disease or congenital defects during pregnancy is unreliable since the axis tends to shift toward the left during the first two trimesters and to return toward the right during the third trimester and since accurate average corrections for this shift can not now be made.

2. Serial electrocardiograms throughout pregnancy on a sufficiently large number of normal women are required in order to determine accurately the variable limits of axis deviation during pregnancy.

3. Inverted Lead III is of no significance, probably being due to transverse position of the heart.

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NOTES ON HEART FAILURE

WITH REPORT OF A CASE OF PURE LEFT VENTRICULAR FAILURE*

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IN SPITE of the vast amount of work that has been done on the physiology of cardiac failure our knowledge of the subject is still largely empirical, and our drug therapy, satisfactory as it is in most instances, is none the less very far from being strictly scientific. By drawing upon the store of accumulated experience we are enabled to classify our cases after a fashion and to treat them more or less successfully, but until we encounter a refractory case we do not realize how often we are saved from therapeutic defeat by the fact that our sovereign remedy, the foxglove, is applicable to almost all varieties of heart failure. The fact is that we are as much at a loss to explain why digitalis usually succeeds as we are to understand why it occasionally fails. We are told that digitalis decreases the cardiac output in normal men and dogs,^{1, 2, 3, 4} but increases it in cardiac failure,^{5†} which would be no less convincing if it were less paradoxical. The validity of the old assumption that heart failure always means diminished cardiac output has recently been questioned seriously. As Wennekebach⁷ says, there is almost an oppressive unanimity in the statements coming from all sides that under certain circumstances the cardiac output may be normal or actually increased. If this be true, is the effect of digitalis on cardiac output in heart failure invariably the same, or does it vary, and what determines its mode of action?

Our clinical experience with the mercurial diuretics has taught us that there must be peripheral, as well as cardiac, factors in what we call "heart failure," and the work of Eppinger, Kisch and Schwarz,⁸ and Harrison and Pilcher,^{6, 9} to mention but a few, has shown that such is actually the case. The effect of edema on the utilization of oxygen by the tissues and on minute-volume blood flow, incomplete resynthesis of glycogen into lactic acid by the skeletal muscles, with all the ensuing metabolic disturbances, and variations of the circulating and noncirculating blood volume, are some of the peripheral factors which must be taken into account. The idea that heart failure cannot be explained on a simple hydraulic basis is not new.¹⁰

To assimilate the often contradictory experimental data and apply them successfully to the problem of untangling the snarl of cardiac, renal, vascular, lymphatic, respiratory and cytological factors in heart

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†The dissenting opinion of Harrison and Pilcher⁶ is based on indirect evidence.

failure is a feat which surpasses even the ingenuity of Wenckebach.⁷ The one thing which is needed, above all other things, to lead us out of this wilderness and start us on the road toward a rational understanding of heart failure is a sufficiently accurate, clinically applicable method of measuring cardiac output.^{10, 11, 12}

The following case of pure left ventricular failure not only illustrates some of the difficulties which beset the clinician in his endeavor to analyze heart failure into its component physiological factors, but nearly epitomizes the entire problem.

CASE REPORT

History.—The patient was a physician, aged sixty-one years. His principal complaint was of air hunger, which he noticed for the first time in the early summer of 1931, while playing golf; the attack was not severe and did not last long. Thereafter on several occasions he felt a little short of breath at night, without any antecedent physical exertion, but the warning was so slight that he disregarded it. The first really alarming attack occurred in July, 1931, while the patient was touring in the East. One night after retiring he became so short of breath that he was compelled to sit up in bed, and for about an hour he suffered from a feeling of substernal tightness and inability to breathe. After the symptoms subsided he felt none the worse, and was able to resume his trip the next day.

One day in August, 1931, while the patient was reclining on the couch after luncheon, his left arm and leg suddenly became numb. There was no involvement of the face, or of speech, and he was able to rise and walk immediately, but subjective sensory disturbances persisted in the arm and leg for several days, and were attended with impairment of dexterity in the use of the hand. When he was examined a few days later his arterial pressure was found to be 215/138 mm. Hg, but no objective neurological signs were demonstrable. The patient did not know when his blood pressure first began to manifest an upward tendency. It had been measured once in 1930, at which time the systolic level stood at 180 mm. Hg, but beyond this no information was forthcoming. For some time he had been finding it necessary to get up once or twice each night to pass urine, and after his August experiences he began to examine his urine occasionally. He found that it usually contained a small amount of albumin and now and then a few hyaline casts.

By the latter part of November, 1931, the patient was noticing slight air hunger on exertion. At the hospital where he visited his patients he was content to wait for the elevator, instead of climbing the stairs as had been his custom. Later in December the attacks of subjective respiratory distress began to return, chiefly at night, and quite apart from physical exertion. Again the sensation was one of substernal constriction and inability to breathe. He had the feeling that he would obtain relief if he could bring up something from his lungs, which was true to a limited extent, but his efforts to raise sputum were seldom successful, and the amount was always very small. The sputum was never bloody. He found that he was more comfortable sitting up and leaning forward than in any other position. He had no pain anywhere at any time. The symptoms did not abate spontaneously, as on former occasions, but grew steadily worse, so much so that for a period of ten days prior to his admission to the University Hospital he had scarcely any repose, day or night. The feeling of tightness in his chest was always present, increasing at times to such an extent that he feared it would strangle him.

Physical Examination.—At first the patient seemed convinced that he was suffering from bronchial asthma; he had already been subjected to skin sensitization

failure is a feat which surpasses even the ingenuity of Wenckebach.⁷ The one thing which is needed, above all other things, to lead us out of this wilderness and start us on the road toward a rational understanding of heart failure is a sufficiently accurate, clinically applicable method of measuring cardiac output.^{10, 11, 12}

The following case of pure left ventricular failure not only illustrates some of the difficulties which beset the clinician in his endeavor to analyze heart failure into its component physiological factors, but nearly epitomizes the entire problem.

CASE REPORT

History.—The patient was a physician, aged sixty-one years. His principal complaint was of air hunger, which he noticed for the first time in the early summer of 1931, while playing golf; the attack was not severe and did not last long. Thereafter on several occasions he felt a little short of breath at night, without any antecedent physical exertion, but the warning was so slight that he disregarded it. The first really alarming attack occurred in July, 1931, while the patient was touring in the East. One night after retiring he became so short of breath that he was compelled to sit up in bed, and for about an hour he suffered from a feeling of substernal tightness and inability to breathe. After the symptoms subsided he felt none the worse, and was able to resume his trip the next day.

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Physical Examination.—At first the patient seemed convinced that he was suffering from bronchial asthma; he had already been subjected to skin sensitization

was no retention of nonprotein nitrogen, but renal resourcefulness was reduced 58 per cent as determined by the urea clearance method. The blood Wassermann and Kahn reactions were negative. There was no anemia.

Summary.—History of paroxysmal nocturnal cardiac dyspnea, moderate air hunger on exertion, cerebral hemorrhage, high blood pressure, nocturnal diuresis, and albuminuria. Presence of air hunger and dyspnea, high arterial pressure, enlargement of the left ventricle, evidences of stasis in the pulmonary circuit without stasis in the greater circulation, widespread arteriosclerosis including electrocardiographic indications of coronary sclerosis, and relative renal insufficiency.

Diagnoses.—Pure left ventricular heart failure, with interstitial pulmonary stasis, but without actual pulmonary edema. General arteriosclerosis, including the arch

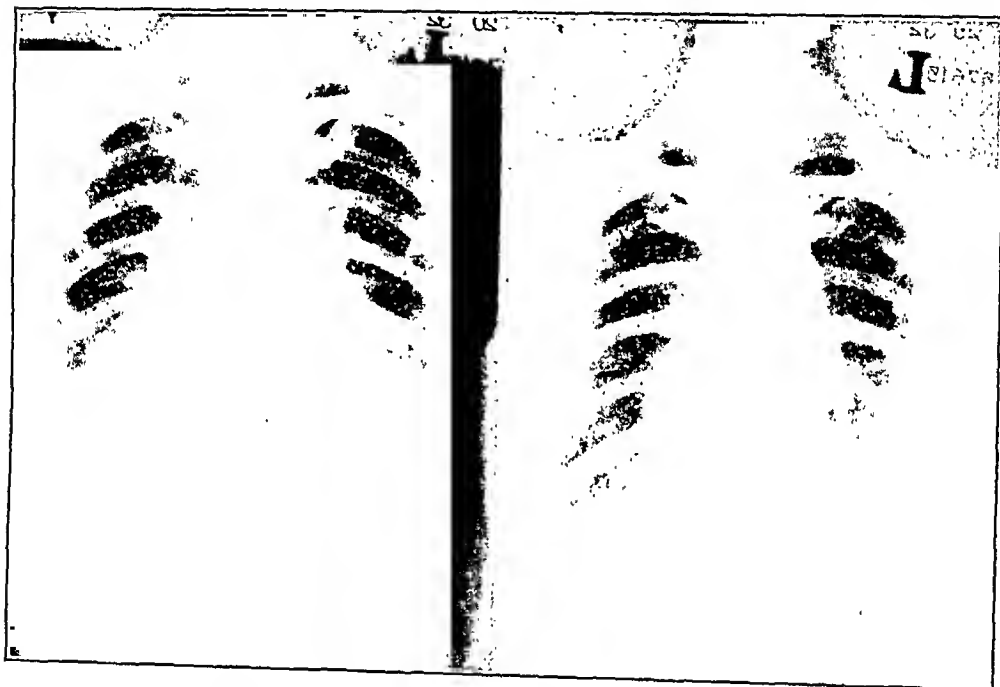


Fig. 1.

Fig. 2.

Fig. 1.—First teleroentgenogram, showing the intrapulmonic stasis and bilateral pleural effusion. (Reproduction has somewhat exaggerated the original intensity and extent of the lung shadows.)

Fig. 2.—Second teleroentgenogram, five days later. The signs of intrapulmonic stasis have disappeared.

of the aorta, the coronary, retinal, and cerebral arteries, and arteriolar nephrosclerosis.

Subsequent Course.—No very satisfactory results followed the use of nitrites, epinephrine, morphine, or whiskey, although transient symptomatic improvement occurred once or twice. As soon as a rational diagnosis was made, 0.5 mg. of strophanthine was given intramuscularly, and on the following day the administration of digitalis leaves in doses of 0.1 gm. three times a day, and of euphyllin in doses of 0.2 gm. three times a day, was begun. Within a few hours after receiving the strophanthine the patient felt immensely relieved, and noticed the onset of profuse diuresis. Improvement continued steadily, and four days later the patient was a different man. All the agonizing sense of constriction of the chest and respiratory distress had disappeared, the ashen hue and anxious look were gone, there had been a weight loss of 5.5 pounds net, the vital capacity had risen from 2300 to 4000 c.c., the left ventricle was definitely smaller, and the pleural fluid and roentgenological

evidences of intrapulmonic stasis had vanished (Fig. 2). Incidentally, the arterial pressure had fallen to 170/120 mm. Hg.

The roentgenograms had shown elongation and dilatation of the aorta, and more careful examination just before the patient was discharged revealed all the usual indications of increased accessibility of its ascending and transverse portions, together with an aortic systolic murmur which had not been present at the first examination. This murmur can best be explained as the result of reduction in the diameter of the vestibular portion of the left ventricle consequent upon recovery from cardiacetasis, the diameter of the aortic orifice and ascending aorta remaining unchanged throughout.

DISCUSSION

The most interesting features of this case were the behavior of the arterial pressure, the respiratory symptoms, the unusual character of the intrapulmonic stasis.

It might readily be assumed that high peripheral resistance was the primary cause of the left ventricular failure, and that interference with coronary blood flow acted as a contributory factor. Physiologists tell us (cf. Wiggers¹³) that when the heart is in prime condition it responds to increased resistance with increased initial and maximal tension and increased diastolic volume. The latter is a tonogenic, or physiological, dilatation. As a result the output of the ventricle remains the same, or even increases, and the duration of systole is actually shortened. This is the first phase of cardiac strain. The damaged heart responds in the same way, but soon passes into the second phase of strain, during which its inherent contractility suffers. The next stage is that of myogenic, or pathological, dilatation, characterized by diminished output. Failure begins when the heart receives more blood than it discharges. At this point stasis appears proximal to the ventricle, and systemic arterial pressure would fall considerably were it not for a "compensatory" vasoconstriction. Vasoconstriction occurring at this juncture could not possibly be genuinely compensatory, for it would create a vicious circle with the failing ventricle, besides producing peripheral disturbances. It is here that clinical experience and physiological predications part company. How can failure avoid growing progressively worse if the ventricle must continue opening the aortic valve against a very high diastolic pressure? How broad is the interjaacent ground between moderate failure with stasis and sustained high arterial pressure on the one hand, and complete failure with falling pressure on the other? It is difficult to understand how patients can linger indefinitely in this intermediate state. Clinical experience does not confirm the dictum that arterial pressure always tends to fall as heart failure develops; cases such as this, in which the pressure remains very high in spite of desperate symptoms, are too common. If anything were needed to confuse matters further, it is furnished by the fact that as soon as recovery begins pressure falls, sometimes considerably below the pre-failure level, and one gains the impression that the fall is the result, rather than the cause, of recovery.

At least we are well rid of the old taboo against giving digitalis when arterial pressure is high.

If diminished cardiac output and secondary vasoconstriction are invariable consequences of left ventricular failure, why are there not plain evidences thereof, such as coldness and cyanosis of the hands and feet, and perhaps lowered pulse pressure? What is the relationship between heart failure and the temperature of the body surface? Other things being equal, why is it that some patients have cold hands and feet, whereas others exhibit extremities that are normally or even excessively warm?

A priori considerations suggest that pure unilateral heart failure, particularly of the left ventricle, should be rather common, but as a matter of fact it is rarely encountered except in the acute form which manifests itself as paroxysmal nocturnal cardiac dyspnea. It is characterized as a rule by relatively more severe respiratory symptoms than bilateral failure, the reasons for which are not clear in every case. The air hunger and dyspnea of the paroxysmal nocturnal seizures are generally proportional to the degree of intrapulmonic stasis and edema, and are regarded as the natural consequence of inability on the part of the left ventricle to handle the volume of blood which is being sent in normal quantities into the pulmonary circuit by the right ventricle. It is therefore to be inferred that the symptoms would be alleviated, at least partially, if the output of the right ventricle were to diminish. In the case here described, however, although the air hunger was moderately severe, it was no worse than it might have been in a comparable case of bilateral failure. The ventilatory capacity of the lungs was at all times adequate to the needs of the patient as long as he remained at rest. His shortness of breath was therefore not referable directly to impaired extensibility of the lungs, but presumably to vagus reflexes contingent upon diminished vital capacity.¹⁴ Thus it is very unlikely that the supervention of right ventricular failure would have ameliorated his air hunger to any appreciable extent. On the other hand, the patient's terrible dyspnea, his acute sense of substernal constriction, and his vivid premonition of death were not only out of all proportion to his air hunger, but were far more intense than would be expected in bilateral heart failure of comparable degree. This conjunction of extreme dyspnea with relatively mild air hunger in pure left ventricular failure was one of the most noteworthy and most inexplicable features of the case. Whenever a critical analysis of respiratory symptomatology is attempted, it is imperative to distinguish sharply between air hunger and dyspnea. Morawitz and Siebeck¹⁵ called attention to this fact in 1909, and it has been re-emphasized repeatedly. No better example could be adduced than the case under discussion.

In any case of heart failure it is impossible to apprehend fully the part played by the left ventricle without spirometric estimation of the

vital capacity to determine the extent to which lung extensibility has been reduced by stasis in the pulmonary circuit. This is especially true in a case such as this, in which the stasis remained confined to the interstitial tissues. How pulmonary stasis can be purely interstitial, besides being extensive enough to reduce lung extensibility 50 per cent and produce air hunger and severe dyspnea without at the same time interfering with transpiration of gases across the alveolar membrane to the extent of inducing pronounced hyperpnea and cyanosis, is a mystery.

Further progress toward answering such questions as have been expressed or implied in this discussion awaits the introduction of a satisfactory method of measuring cardiac output in health and disease. Without such a method our knowledge of the physiology of heart failure stands at dead center, as did the physiology of diabetes before the discovery of insulin.

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NOTE ON THE TRANSMISSION OF AORTIC SYSTOLIC MURMURS TO THE ABDOMINAL AORTA*

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SOME months ago while examining a patient with aortic stenosis, it was noted that the murmur was readily heard over the abdominal aorta in the region of the navel. Inasmuch as systolic murmurs in general are propagated best in the direction of the blood stream, the presence of the murmur is readily explained. However, several standard texts were consulted, and in none was there reference to the transmission of murmurs originating at the aortic valves or in the thoracic aorta to the abdominal aorta.

Notes have been collected on twenty-five patients. In eleven of these, a diagnosis of aortic stenosis was made. In nine, the murmur was transmitted to the abdominal aorta, while it was not heard there in two. In five cases of lentic aortitis with aortic insufficiency, having both systolic and diastolic murmurs at the aortic area, all showed transmission of the systolic murmur to the abdominal aorta. One patient with thoracic aneurysm without insufficiency and another with aortic insufficiency each had a systolic murmur over the abdominal aorta. One patient with arteriosclerosis and hypertension had a systolic murmur at the aortic area which was transmitted to the abdominal aorta. In one case of subacute bacterial endocarditis involving the aortic valve, with a to-and-fro murmur at the aortic area, a loud systolic murmur was audible over the abdominal aorta, much louder than that heard over the heart, suggesting the possibility of vegetations in the aorta. A patient with toxic adenoma of the thyroid with substernal extension of the goiter had a very faint systolic murmur audible at the aortic area. Immediately below the ensiform, the murmur was barely audible. It became much louder on approaching the navel and was faintly transmitted to the femoral arteries. The probable explanation of the murmur seemed to be the pressure of the very firm thyroid gland on the thoracic aorta. A patient with long standing adenoma of the thyroid developed malignant changes in the gland, which was largely intrathoracic. Signs of venous pressure were apparent. There were no murmurs over the precordium. A systolic murmur was audible above and below the navel over the aorta. X-ray films, as well as operative and postmortem findings, indicated that the thyroid gland was pressing on the thoracic aorta. A patient with thoracic aortic aneurysm came to autopsy. A murmur had been heard over the abdominal aorta but none over the aneurysm. In addition

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to aneurysm of the arch of the aorta, autopsy revealed atherosclerosis with calcification of the abdominal aorta, which may have contributed to the production of the murmur. Two patients with pernicious anemia, without demonstrable heart disease, had systolic murmurs, presumably "hemic," at the base of the heart. In each, the murmur was audible over the abdominal aorta, though very faint. The red cell counts were 1.5 and 1.2 millions, respectively.

The murmurs heard over the abdominal aorta have been noted in the region of the navel; usually about two fingerbreadths above and below it, and a little to the left of the midline. In most of the patients the murmur was heard best just above the navel. Generally, it was less intense or absent at some point between the navel and the ensiform. In one patient with aortic stenosis and in one with intrathoracic goiter, the murmur could be heard along the abdominal aorta, over the common iliac and femoral arteries. In one with lentic aortic insufficiency, a systolic murmur was heard over the aortic valve area, abdominal aorta and iliaes.

Compression of the aorta with the bell of the stethoscope must be avoided, though it is essential that the instrument be near the vessel. Failure to hear a murmur over the abdominal aorta in obese individuals may be due to the interposed layer of fat. In one patient with an aortic systolic murmur whose abdomen was distended and whose abdominal muscles were resistant, no murmur was heard; but when pressure was exerted with hands above and below the navel, the bell of the stethoscope was more nearly approximated to the aorta and a murmur was then audible. If one auscults over the femoral artery, one finds that considerable pressure is required to produce a murmur. In the average patient with abdomen of normal contour, it requires still greater pressure to produce a murmur over the aorta, and in our experience it is usually impossible to do this.

As a control, a series of 50 normal individuals has been examined. In none was a murmur audible over the abdominal aorta, and in only one, with very thin abdominal walls, was a murmur produced by pressure of the bell of the stethoscope. In examining patients with scaphoid abdomen, pressure with the bell of the stethoscope during auscultation over the aorta may produce a murmur and, therefore, must be avoided, since such a murmur has no diagnostic significance.

The intensity and quality of the cardiac murmur do not appear to be the sole factors which determine its transmission. When the abdominal aortic murmur is louder than that heard over the aortic valves, or when no thoracic murmur is detected, an extra-cardiac cause for the murmur, such as aneurysm, intrathoracic goiter or mediastinal neoplasm, should be looked for, in the absence of a demonstrable abdominal lesion.

A systolic thrill was found at the aortic area in association with the

murmur in many instances, particularly in aortic stenosis. But murmurs producing no palpable thrill are audible over the abdominal aorta quite as frequently as those associated with a thrill, so far as we can determine from this small series of cases.

These observations demonstrate that systolic aortic murmurs, regardless of their cause, are frequently transmitted from the aortic valves or thoracic aorta to the abdominal aorta. The finding of a murmur over the abdominal aorta is of no differential diagnostic value as to the type or etiology of a lesion of the aortic valves. In fact, a systolic murmur originating from a thoracic aneurysm or from external pressure on the thoracic aorta may be transmitted with the blood stream to the abdominal aorta. In some instances the murmur may not be detected over the thorax. In no case were diastolic cardiac murmurs heard over the abdominal aorta.

Systolic murmurs are frequently encountered in connection with aneurysm of the abdominal aorta. Any abdominal lesion causing pressure on the vessel and producing a relative stenosis may also cause a systolic murmur. The fact that similar murmurs may originate at the aortic valves or in the thoracic aorta should be kept in mind in connection with the diagnosis of abdominal lesions.

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OCCURRENCE OF SUBACUTE BACTERIAL ENDOCARDITIS IN MITRAL VALVULAR DISEASE WITH PREEXISTING AURICULAR FIBRILLATION*

A CASE REPORT

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SOME years ago Libman¹ made the observation that patients suffering from chronic valvular disease with auricular fibrillation rarely developed subacute bacterial endocarditis. Subsequently he, Rothschild, and Sacks² studied the disturbances of cardiac mechanism in 123 cases of this disease. Auricular fibrillation was encountered only once during the active stage of the disease, and in that patient the rhythm had been normal until three days before death. Three other cases had already progressed to the bacteria-free stage. Their observations of patients with fibrillation convinced them that once this arrhythmia was permanently established, there was little danger of subacute bacterial endocarditis supervening. The observation that auricular fibrillation and active subacute bacterial endocarditis are mutually exclusive, save in an exceptional instance, they considered of diagnostic value.

Thayer,³ in a series of fifty-two cases studied up to the fatal issue, noted auricular fibrillation in three instances. However, in one of the three, the arrhythmia appeared eight days before death. In the other cases no statement was made of the duration of this disorder of rhythm. Recently (1930) Thayer⁴ stated that auricular fibrillation was noted in 5 per cent of a series of 100 cases of subacute streptococcal endocarditis studied until death.

Sprague⁵ referred to one case in which auricular fibrillation had been present four years before the onset of the infection. The arrhythmia was abolished by the use of quinidine sulphate, but recurred six months before death at the time of the appearance of the infection.

Fulton and Levine⁶ in their series of 111 cases, of which thirty were examined at necropsy, encountered auricular fibrillation only once and then as a terminal event.

Blumer⁷ referred to 301 case records in which auricular flutter was encountered once, and auricular fibrillation four times. He noted that many of the records antedated the use of instruments suitable for accurately distinguishing arrhythmias.

Elsewhere we⁸ have reported observations of two cases of subacute bacterial endocarditis showing many disturbances of the cardiac mech-

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anism. In one instance paroxysmal auricular flutter was recorded by electrocardiograms. While transitory disturbances of A-V conduction are not extremely rare, the occurrence of subacute bacterial endocarditis (*Streptococcus viridans*) in a patient with chronic rheumatic valvular disease and established auricular fibrillation is sufficiently unusual to warrant study of the following case.

CASE REPORT

The patient, I. G., was first enrolled in the Third (N. Y. U.) Medical Division Cardiac Clinic on November 1, 1929. She was twenty-four years old, a widow, and mother of four children. Her chief complaints were dyspnea and fatigue, cough, with occasional hemoptysis, epistaxis, palpitation, and slight precordial pain, all of about one year's duration. She had noticed slight swelling of her ankles since 1923. Recently she had occasional vertigo and "spells of feeling faint." In her past history she stated that she had had typhoid fever and pneumonia at four years, scarlet fever and tonsillitis at five years, measles and diphtheria at six years, whooping cough at nine years, and influenza at fourteen years. Heart disease was first discovered by a physician sometime between 1909 and 1913. Her family history is of interest because both her father and a brother died of heart disease, the former at fifty-three years, the latter at nineteen years.

On admission to the clinic in 1929, physical examination showed the patient to be well developed, obese, and neither dyspneic nor cyanotic. No subcutaneous nodules or petechiae were discovered. Pupillary reactions were normal. Examination of the heart revealed the maximum apical impulse in the fifth left intercostal space outside the midclavicular line. The sounds were of fair quality. There were a harsh, blowing systolic murmur and a rumbling, diastolic murmur accompanied by a diastolic thrill at the apex. A soft systolic murmur was heard at the base. P_2 was greater than A_2 . The rhythm was totally irregular. The ventricular rate was 77, the pulse rate was 68. The blood pressure was 116/76 mm. The lungs were clear; liver and spleen were not palpable. There was no edema or clubbing of the fingers. Electrocardiograms showed auricular fibrillation. A teleroentgenogram showed an enlarged heart with accentuation of all the cardiac curves, especially the pulmonary artery and left auricular curves. Wassermann test was negative. The urine examination was negative, except for a trace of albumin.

The patient was digitalized and given a daily maintenance dose of 3 grains of digitalis (whole leaf). She attended the clinic about once a month. Auricular fibrillation persisted. The temperature ranged between 99° and 100.2°. Several months later she developed pain in the left shoulder which was intermittent during the next six months. At times the patient felt better, but she was never free of symptoms or fever. In December, 1930, the patient developed cough with gripe-like symptoms which gradually subsided, but reappeared in March, 1931. In May, 1931, arthritis of an ankle joint developed and was followed by involvement of the fingers of one hand. She gradually became worse, developed dyspnea at rest, cough and fever (101.4°) and complained of pain in the left shoulder and right ankle. At this time it was noticed that her complexion had changed, having become pale and pasty. Edema of the legs appeared. On her visit to the clinic on June 19, 1931, she complained of dizziness, fever, and pain in the extremities. The spleen was palpable. The ventricular rate was 100; pulse rate, 86. The patient was referred to the hospital that evening.

Admission to the Hospital.—The patient entered the hospital on June 24, 1931. On admission she complained of aching pain in the right shoulder, elbow, and right wrist joints, fever at night, dyspnea, and fatigue. Physical examination revealed

orthopnea of choice, moderate pallor, slight cyanosis of the lips and finger nails. Her fingers appeared to show slight clubbing (the patient herself said that they were formerly more tapered). The mucous membranes were pale and no petechiae were visible. The fundi showed no changes. Veins of the neck were not dilated. The lungs were clear. Examination of the heart revealed essentially the same findings as noted in the clinic. The rhythm was still totally irregular. The liver was palpable; the spleen was easily palpated and was tender. There were no signs of ascites. The extremities showed no edema. On the thenar eminence of the right hand there were two bluish spots which were not tender. The admission diagnosis was as follows: Cardiac*—(a) Unknown (rheumatic?) inactive and active (possibly subacute bacterial endocarditis), (b) enlarged heart, mitral stenosis, mitral insufficiency (possibly bacterial endocarditis), (c) auricular fibrillation, (d) Class III. Accompanying this diagnosis was a note written by the house physician, Dr. Marshall Brown, which we quote verbatim, "The fact that the patient has auricular fibrillation is against the diagnosis of bacterial endocarditis, but the marked anemia, fever of six weeks' standing, palpable spleen, and questionable petechiae on the right hand make this diagnosis one to be considered."

Subsequent Observations and Course in the Hospital.—Examination by one of us later revealed essentially the same findings. Pallor was marked although not of typical "café au lait" color. Petechiae were visible in the mucous membrane of the left cheek, and a small tender red area was found on the tip of the middle finger of the left hand (Osler node). The diagnosis offered was the same as that just mentioned except that we felt more certain of the presence of subacute bacterial endocarditis. A blood culture taken on June 25 was positive for *Streptococcus viridans*. On July 3, the patient experienced a sharp, agonizing pain in the left upper quadrant of the abdomen which did not radiate. Examination of the abdomen revealed marked rigidity, pain and tenderness over this area. There were no accompanying urinary symptoms. Splenic infarction was added to the diagnosis. Another blood culture, taken on June 30, showed numerous colonies of *Streptococcus viridans*.

Laboratory Data: 3,410,000 red blood cells; hemoglobin, 70 per cent; 7,600 white blood cells with 80 per cent polynuclears and 20 per cent lymphocytes. Blood Wassermann was negative; blood N. P. N. 34 mg. per cent; sugar, 115 mg. per cent; creat. 1.5 mg. per cent. All electrocardiograms showed auricular fibrillation. A urine sediment count (Addis)† was done with the following results: twelve hour vol. 296 c.c.; specific gravity, 1011; P_{II} 5.8, albumin negative; red blood cells 1,480,000; white blood cells, 5,032,000; casts, 79,900.

The patient grew progressively weaker, more anemic, and lost weight continuously. A third blood culture was also positive for *Streptococcus viridans*. On July 13 the patient insisted upon going home, leaving the hospital at her own risk. She was readmitted two weeks later, to another medical service, complaining of palpitation, weakness, fainting spells, chills and fever. From this time to death on August 6, the patient ran a downhill course, the outstanding feature of which was the increasing evidence of sepsis. The temperature fluctuated daily between 99° and 104° (F). There were no new physical findings. Final clinical diagnosis was: Cardiac—(a) Unknown (rheumatic fever?) inactive, bacterial endocarditis, *Streptococcus viridans*; (b) enlarged heart, mitral stenosis and insufficiency, bacterial endocarditis of mitral valve; (c) auricular fibrillation; (d) Class III. II. Focal embolic glomerulonephritis. III. Splenic infarction.

Necropsy Report.—The following is a résumé of the significant pathological find-

*Cardiac diagnosis conforms to the nomenclature recommended by the American Heart Association.

†Normal values for twelve-hour specimens should not exceed: red blood cells 500,000; white blood cells, 1,000,000; and casts up to 5000.

ings. The skin had a sallow tint. Two pinpoint, brownish spots resembling old petechial hemorrhages were found on the dorsum of the left hand. Another was seen at the base of the right thumb. In the conjunctival sac of the right eye, there was a linear brownish area on the temporal side about 4 mm. in length. The ankles presented a moderate degree of pitting edema. The peritoneal cavity contained no fluid. The left pleural cavity contained about 500 c.c. of clear amber fluid, and about 300 c.c. of similar fluid were found in the right pleural sac.

Heart.—On opening the pericardium, firm bands of fibrous tissue were found irregularly distributed and binding the parietal and visceral pericardium. The heart



Fig. 1.—Photograph of heart to show marked dilatation of the left auricle, mural endocarditis of the left auricle and the old and recent lesions of the mitral valve.

weighed 470 gm. It presented marked dilatation of the left auricle. The right auricle appeared to be intact. The leaflets of the tricuspid valve were thin, translucent, and their chordae tendineae were delicate and shortened. The right ventricle showed slight hypertrophy. The pulmonary valves showed no naked eye changes. On opening the left auricle, it was found to be enormously dilated. (Fig. 1.) Its walls were thickened and on the lateral wall was seen a medallion-shaped patch, 4 by 5 cm., raised above the adjacent endocardium for a distance of 1 to 2 mm. Its surface was puckered, wrinkled, and composed of firm, pinhead sized verrucae. The auricular appendage appeared normal. The mitral orifice was stenotic, admitting two fingers. The valve showed marked thickening and fusion of the chordae tendineae, which were also shortened. The attached papillary muscles were notably hypertrophied. The aortic cusp of the mitral valve was the seat of a vegetative process

in which firm thrombotic material extended over both surfaces of the valve, and pedunculated vegetations reached into the ventricular chamber (Fig. 1). On the posterior cusp, a few thrombotic vegetations were also found. In addition, several small verrucae were noted. The vegetations appeared to be fairly well organized and were not friable. In the aortic leaflet calcific material could be palpated. The left ventricle showed moderate hypertrophy. The aortic valve was the seat of thrombotic vegetations which were found chiefly over the corpora arantii. These vegetations were small, polypoid, fairly firm, and quite irregular in shape. There was a slight degree of fusion in the commissure between the right coronary cusp and the non-coronary cusp. The coronary arteries appeared to be well preserved. The heart

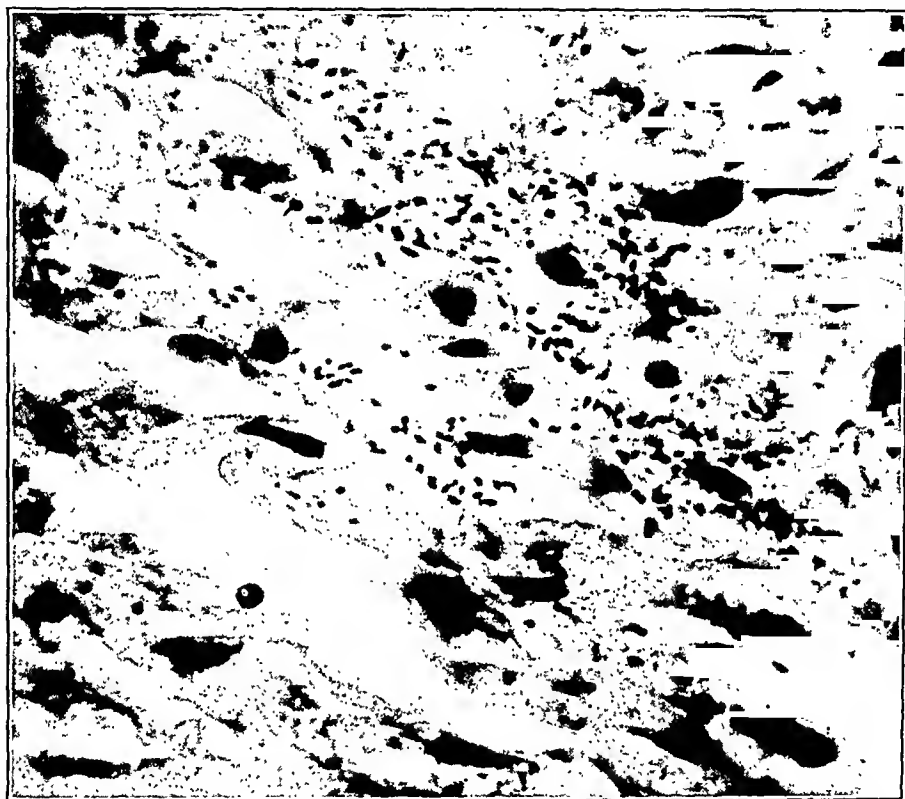


Fig. 2.—Photomicrograph (x1000) to show cocci in the depths of the vegetation on the aortic leaflet of the mitral valve.

muscle on section was pale, brownish red, and somewhat flabby. The aorta and pulmonary arteries were well preserved and showed only focal atheroma.

Lungs.—Except for bilateral adhesive pleuritis and moderate congestion and edema, no noteworthy abnormalities were noted. *Spleen*: In the spleen, which measured 18 × 8 × 8 cm., there was found a cystic infarct, occupying the lower one-third of the organ. The cut surface was mottled green and purple, and revealed several infarcted areas. The lower pole was converted into a large necrotic cavity filled with homogeneous, foul-smelling, brownish material. *Liver*: Was enlarged and showed the markings of chronic passive hyperemia. *Kidneys*: Both kidneys were slightly enlarged and showed numerous anemic infarcts, chiefly cortical in distribution. No petechiae were noted. The other organs showed no especially significant changes.

Microscopic Report.—*Heart and great vessels*: Section through the wall of the left auricle showed marked thickening of the endocardium and numerous focal areas of cellular infiltration between the endocardium and the underlying auricular muscle.

A section through the area of endocarditis in the left auricle showed verruca formation. Sections of the mitral valve showed an ancient valvulitis with deposition of fibrous tissue which had become hyalinized. Blood channels were very numerous and arterioles showed advanced sclerosis. Sections through the vegetations showed infiltration by cells of all types, but chiefly histiocytic cells which extended freely into the thrombotic vegetations. Evidence of organization was seen in the infiltration by fibroblasts into the deeper parts of the thrombi. Gram-positive cocci were demonstrable in the sections through the vegetations on the aortic leaflet of the mitral valve (Fig. 2); none were seen in the sections through the posterior cusp or in the auricular lesion. Sections of the aortic valve showed sclerotic changes in the base and the free margin of the valve, suggesting previous mild focal inflammation. A section through the vegetation showed it to consist chiefly of fibrin with an inflammatory base composed of edematous collagen fibers and histiocytes, a few polynuclear leucocytes, and a few lymphocytes. Gram-positive cocci were demonstrated in the superficial layers of the vegetation. Sections of the other valves showed no inflammatory changes. Sections of the aorta and pulmonary artery were negative. Sections of the myocardium showed occasional areas of perivascular fibrosis. Occasionally intrafascicular scarring was encountered, but it was not marked except in the sections of the papillary muscles. No Aschoff nodules were found.

Kidneys.—Sections of both organs taken from areas adjacent to infarcts showed severe tubular degeneration with complete loss of nuclei, many tubular hemorrhages and much desquamated material in the tubular lumina. The glomeruli were so altered by the diffuse infarction that differentiation of embolic lesions was impossible. No bacterial masses were encountered.

Examination of the other organs confirmed the naked eye diagnosis.

Final Pathological Diagnosis.—*Heart:* Hypertrophy and dilatation; bacterial vegetative endocarditis (*Streptococcus viridans*), mitral and aortic valves; chronic valvulitis of mitral valve; mitral stenosis and insufficiency, verrucous thromboendocarditis of left auricle; chronic adhesive pericarditis; fibrosis of myocardium. *Spleen:* Multiple infarction with necrosis. *Kidneys:* Multiple bilateral infarctions. *Liver:* Chronic passive hyperemia. *Lungs:* Chronic passive hyperemia; edema; chronic adhesive pleuritis, bilateral.

COMMENT

Certain facts of clinical interest observed in this patient's course are worthy of emphasis. Thus we have proof of the existence of established auricular fibrillation for twenty-one months prior to death. From the patient's history a clue to the possible previous existence of this rhythm is found in her complaint of palpitation which began one year prior to entrance in the cardiac clinic.

It might be argued that bacterial endocarditis was present in this patient when her symptoms brought her to the cardiac clinic. Against this interpretation are the negative findings noted especially in her clinic visits: no splenomegaly, no petechiae, no clubbing of the fingers, no change in complexion, and no subjective complaint of fever until a new set of symptoms appeared in December, 1930, nine months before death. At this time "grippal" symptoms appeared, slowly subsided, and reappeared in March, 1931, five months before death. With the recrudescence of symptoms of weakness, fleeting joint pains, fever, increased fatigability, and the appearance of pallor, her clinical picture

took on a new aspect. Thereafter we find the development of all the confirmatory signs necessary to establish the diagnosis of subacute bacterial endocarditis. From this analysis the conclusion seems reasonable that auricular fibrillation was present for a considerable period (at least one year) before the onset of the terminal infective process.

The question of relationship between the occurrence of subacute bacterial endocarditis and advanced mitral stenosis has recently been studied by Sprague⁵ and Fulton and Levine.⁶ These observers agree that subacute bacterial endocarditis is rarely encountered in patients with advanced mitral stenosis. The case here presented showed signs of mitral stenosis and insufficiency in life. At necropsy the mitral valve measured 10 cm. in circumference at its base. It was rigid and the orifice was definitely, though *moderately*, stenotic. The shortened, thickened, fused chordae tendineae gave evidence of incompetency as well. The vegetations were hardly large enough to add to the degree of stenosis.

Thus in accord with the observations mentioned this patient did not have *advanced* mitral stenosis, although such might have been anticipated because of preexisting auricular fibrillation. It is interesting in this connection to note that in Sprague's cases the one patient with auricular fibrillation also had a wide mitral valve orifice, measuring 15 cm. in circumference. Any parallelism which might be drawn from the infrequency of the association of subacute bacterial endocarditis and advanced mitral stenosis on the one hand and auricular fibrillation on the other would have to take into account the frequency of auricular fibrillation in the various grades of mitral stenosis.

SUMMARY

A case of subacute bacterial (*Streptococcus viridans*) endocarditis is reported because of the occurrence of this disease in a patient with established auricular fibrillation associated with chronic rheumatic valvular disease.

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EFFECT OF ASPHYXIA AND OF ANOXEMIA ON THE ELECTROCARDIOGRAM*

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THE changes in the electrocardiogram taking place during experimental asphyxia have been the subject of several investigations by different observers.^{1, 2, 3, 4} The results of these observations are not, however, concordant. The clinical as well as experimental understanding of the effect of asphyxia on the electrocardiogram is of an obvious importance. A better knowledge of the effect of asphyxia on the electric potential of the heart would assist in separating many complex and hitherto obscure points of cardiac disease as recorded by the electrocardiogram. Particularly is this true clinically, as asphyxia and anoxemia are usually accompanying factors of heart disease.

The experiments described in the present communication were performed with the object of securing further information on this problem.

Before proceeding with a description of the methods used and of the results obtained it is necessary to define with somewhat greater precision the rather general term of asphyxia. Under asphyxia is understood a complex condition resulting (a) from an acute diminution of oxygen supply to an animal or one of its organs and simultaneously (b) from a diminished removal of the products of metabolism produced by the animal or organ. In other words asphyxia of an organ consists of a state of anoxemia complicated by an accumulation in the organ, i. e., in the blood perfusing it, of carbonic acid and lactic acid together with various other normal and abnormal products of metabolism. The method of the previous observers has been either to obstruct the blood flow through the coronary blood vessels⁵ or to produce a general asphyxia of the whole animal.⁶ In our experiments we endeavored to study the effect of asphyxia as well as of its component parts separately so as to determine which aspect of the asphyxial condition is chiefly responsible for the changes in the electrocardiogram.

All experiments of previous observers in this field have been done on the intact animal. It is obvious that in order to study the direct effect of asphyxia on the heart it is necessary to rule out all possible effects which asphyxia may exert on the heart indirectly, for instance through the central nervous system or by changing the blood pressure. The

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necessary control can only be achieved in experiments performed on the heart lung preparation.

All our experiments were performed on dogs from eight to ten kilograms in weight. The animal, after injection of a small dose of morphine, was anesthetized with chloroform and ether mixture, placed in position on the board, and its electrocardiogram was taken with standard leads before the beginning of the preparation. The heart-lung preparation was then made, and the electrocardiogram was retaken in order to determine whether it showed any changes as result of the operation and especially to determine the angle to which the heart became displaced by the manipulation; in the greater majority of experiments this was entirely negligible. All the experiments were performed at a constant arterial blood pressure and output of the heart. In most cases the arterial pressure was adjusted to 100 mm. Hg and the output to 600 c.c. per minute. Asphyxia of the whole heart was produced in the experiments either by shutting off the respiration or by restricting the blood supply to the heart muscle by severe coronary vasoconstriction following introduction of pitressin into the circulating blood. In some experiments asphyxia was produced by increasing the dead space of the respiratory system and making the animal rebreathe the same air.

Anoxemia of the whole heart was produced by administration of potassium cyanide, and excess of CO_2 by administering blood which had previously been exposed to a definite tension of carbonic acid. Local cardiac asphyxia was produced by temporary clamping of the coronary arteries, or by perfusing them with asphyxial blood removed from another heart lung preparation. In similar manner were also produced local anoxemia and excess of CO_2 .

In prolonged experiments the electrocardiogram was taken at intervals of two minutes; in the case of administration of the quickly acting pitressin and cyanide the records were run continuously.

GENERAL CARDIAC ASPHYXIA

(a) *By Arrest of Pulmonary Ventilation.* After having taken several normal electrocardiograms the respiratory pump would be stopped and the heart-lung preparation was gradually asphyxiated. At a degree of asphyxia which corresponds to 50 per cent oxygen unsaturation of the blood, the heart starts to dilate and the blood pressure drops. The arterial blood pressure could be, however, easily adjusted by means of the variable resistance of the heart-lung apparatus. As asphyxia continues, this adjustment becomes more and more difficult and finally impossible. In some of our experiments asphyxia was carried to the stage at which the arterial blood pressure dropped to about 50 mm. Hg. The asphyxia was terminated either by switching in the respiratory pump or by administration of freshly oxygenated blood. Usually the recovery of the heart was rapid and complete, but in a certain number of cases where

the asphyxia was pushed too far the experiment ended by development of heart-block or of ventricular fibrillation.

The changes observed in the electrocardiogram in asphyxia of the heart lung preparation in the early stages were similar to those noted by one of us in the intact animal.² The usual observation was an elevation or a depression of the R-T interval above or below the isoelectric level of the electrocardiogram. The change in the R-T interval in the present series of experiments on the heart-lung preparation was not very conspicuous. In the early stages of asphyxia, up to the point of about 50 per cent oxygen saturation of the blood, there was usually a progressive diminution in size of the T-wave in all leads. Further deoxygenation of the blood, below 50 per cent, was accompanied by an inversion of the T-wave, usually in Lead I, although inversion of the T-wave in all three leads was not uncommon. At about the same time but sometimes only with further deoxygenation, down to about 25 per cent oxygen saturation, the change in the R-T interval of the electrocardiogram was noted, which progressed with the continuation of the asphyxia. The change consisted usually of a depression of the R-T interval in Lead I and an elevation in Lead III, although sometimes elevation in all leads or a depression in all leads occurred.

Asphyxia in its later stages caused the heart to slow from ten to fifteen beats per minute. This slowing was accompanied by a progressively increasing dilatation of the ventricles. The left side of the organ dilated more than the right during the early stages of asphyxia. An unmistakable dilatation of the left ventricle began with about 40 per cent oxygen saturation of the blood, and, at the time, the T-wave was found to be inverted in Lead I.

Resumption of the respiration or administration of fresh blood at any time before an extreme state of dilatation of the heart was reached caused a complete return of the electrocardiogram to normal. In some severe cases the recovery of the heart had to be assisted by massage.

(b) *By Pitressin.* The vasoconstrictor action of pituitary extract and of pitressin on the coronary blood vessels is very considerable, as has been shown by several previous observers. In fact it is so conspicuous that the organ shows signs of acute deprivation of oxygen and all the symptoms of cardiac asphyxia. In our experiments injection into the general circulation of the heart-lung preparation of 0.5 to 1.0 c.c. (P.D.) of pitressin had an effect very similar in character to that of asphyxia in regard to the general activity of the heart as well as the electrocardiogram. Slowing of the heart usually began forty seconds after injection of the drug and reached its maximum at about seventy seconds when the heart slowed by 10 to 15 beats per minute.⁷ Frequently, especially with the larger doses, a dilatation of the heart was observed. Elevation of the T-wave and of the R-T interval as described previously on the intact animal was a constant feature in these experiments.

GENERAL CARDIAC ANOXEMIA AND EXCESS OF CO₂

Anoxemia was produced either by administration of potassium cyanide in doses which would arrest the oxidative processes or by replacing the normal blood in the apparatus by thoroughly deoxygenated blood. In

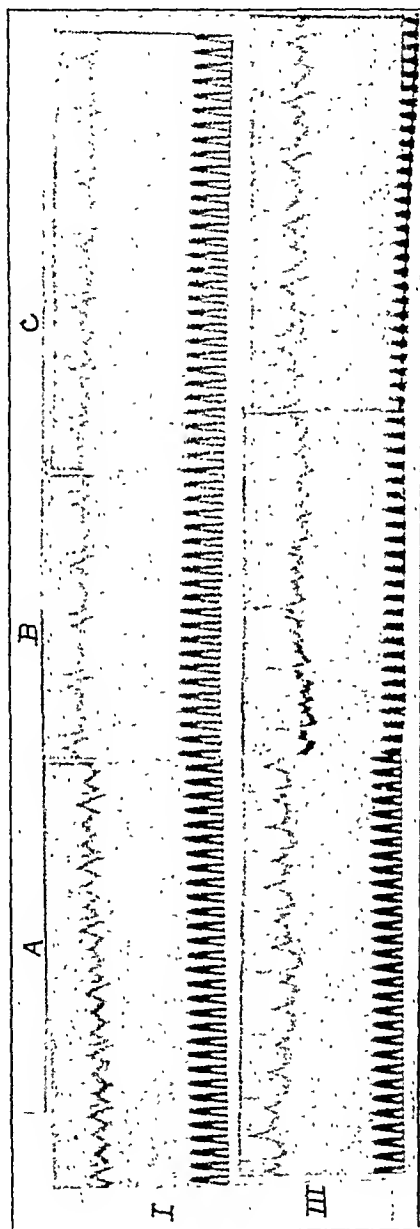


Fig. 1.—The effect of anoxemia on the electrocardiogram. There is a progressive diminution in size and inversion of the T-waves. No change in the R-T interval was noted. A, Leads I and III taken at the beginning of the experiment; B, Leads I and III taken two and three minutes after A; and C, Leads I and III taken five and six minutes after A when the heart had dilated.

neither case were the changes in the electrocardiogram like those observed in asphyxia. The T-wave became small in all leads and remained small until heart-block or ventricular fibrillation ensued. No change in the R-T interval was noted in our experiments, although in some of them anoxemia was allowed to continue until the heart dilated and the blood pressure fell much the same as it did in the case of asphyxia. When fresh blood was substituted for the deoxygenated or for the cyanide

blood before the appearance of complete heart-block or of ventricular fibrillation, the physical appearance of the heart and the electrocardiogram returned to normal.

The effect of CO_2 on the heart was studied by substituting oxygenated blood containing 80 vol. per cent of carbon dioxide ($\text{P}_{\text{H}} 7$) soon after respiration had been shut off. The blood when passed through the heart was collected and was not permitted to flow back into the venous reservoir. Any effect on the electrocardiogram of the reduced oxygen to the heart was thus avoided. There was a marked dilatation of the coronary vessels, and many extrasystoles arose in both ventricles and auricles. The heart dilated when exposed to the increased CO_2 tension and the output diminished. The electrocardiogram showed runs of extrasystoles. The extrasystoles were often so numerous that the curves looked as though the ventricles were fibrillating. However, when arterial blood was substituted for blood containing CO_2 the curves returned to normal. Some of the records showed an increase in ventricular conduction time early in the experiments. The T-waves were high or deeply inverted. No change in the R-T interval was observed.

LOCAL CARDIAC ASPHYXIA ANOXEMIA AND EXCESS OF CO_2

For these experiments the three main branches of the coronary system were carefully dissected as close to their origin as possible. The right coronary artery, the circumflex branch, and the descending branch of the left coronary artery were surrounded by ligatures by pulling on which it was possible to obstruct any of the three branches. Clamping of any of the coronary arteries produced in our experiments varying pictures in the electrocardiogram in different animals. This is most probably determined by the different development of the collateral circulation between the arteries. It has been shown by previous observers that anastomoses in the coronary system, although well developed in the dog's heart, show considerable variations from one animal to another.¹

Repeated clamping of the right coronary artery was performed in twelve animals. In six it showed an increase in size of the T-wave in all leads. In five it produced an increase in the T-wave in Lead I with a decrease or an inversion of the wave in Lead III. In one case the T-wave was found to be inverted in Lead I and high in Lead III. In all cases, however, the R-T segment showed a slight depression in Lead I and an elevation in Lead III.²

Clamping of the circumflex branch of the left coronary artery showed likewise many different effects in regard to the T-wave. The most common one observed was a tendency to a lowering or an inversion of the T-wave in Lead I which was progressive as the period of clamping increased.³ In some instances the T-wave remained unchanged and a change in the R-T segment alone was noted. The R-T interval was elevated in Lead I; this change was usually so marked that the T-wave

branched from the QRS complex. The S-T segment was depressed in Lead III.

Clamping of the descending branch of the left coronary artery produced the most variable changes of all vessels clamped.⁸ Shortening of P-R interval or inversion of the P-wave was of common occurrence. Frequently the heart rate slowed during the period of clamping. Inversion of the T-wave in all leads was usually the common finding, although inversion in Lead I with an elevation in Lead III occurred in a certain number of cases. A conspicuous change in the R-T interval with an elevation in all leads was most common, although an elevation of the S-T segment in Lead III and an inversion of it in Lead I sometimes occurred. An increased duration of the QRS complex was noted in the majority of our experiments indicating an involvement of the conducting system of the ventricles.

Similarly to the case of general asphyxia of the heart muscle, clamping of the coronary artery also produces a conglomerate of changes which cannot be interpreted without further analysis. Too many factors operate simultaneously, and it is again difficult to decide which of them are mainly responsible for the changes in the electrocardiogram. The immediate effect of clamping an artery is an acute drop of blood pressure in the periphery including the capillaries. We consider that this factor is of no significance in regard to the changes observed in the electrocardiogram and this for the following reasons: A sudden drop of blood pressure in the perfused coronary arteries of a heart lung preparation does not bring about any change in the electrocardiogram so long as this drop of blood pressure is not sufficiently prolonged to bring about an asphyxial state. The maximum drop of blood pressure peripherally to the place of clamping is observed within a very short time after the beginning of occlusion. The changes in the electrocardiogram, however, develop gradually and are progressive. The cause of these changes must be looked for among those chemical processes which result on deprivation of the blood supply and lead to fundamental disturbances of the cardiac activity. Similarly to the general asphyxia in the case of clamping an artery, we deal again with anoxemia, with accumulation in the tissues of various known products of metabolism such as carbonic and lactic acids and of other products hitherto unknown but strongly suggested by various observers.¹¹ The following attempts were made to differentiate between the possible factors in order to find the one which is responsible for the change in the R-T segment. The coronary arteries in the heart lung preparation were carefully dissected and prepared for insertion of cannulae.¹² The cannulae were connected with a reservoir containing blood. By raising or lowering the reservoir the blood pressure in the perfused coronary artery could be changed within wide limits. By changing the blood in the reservoir it was possible to perfuse the coronary artery with blood of any desired composition. In all these

experiments the external work of the heart was constant, that is, its output and the arterial resistance remained the same. The blood perfusing the coronary arteries was warmed on the way from the reservoir to the same temperature as the blood entering the cavities of the heart.

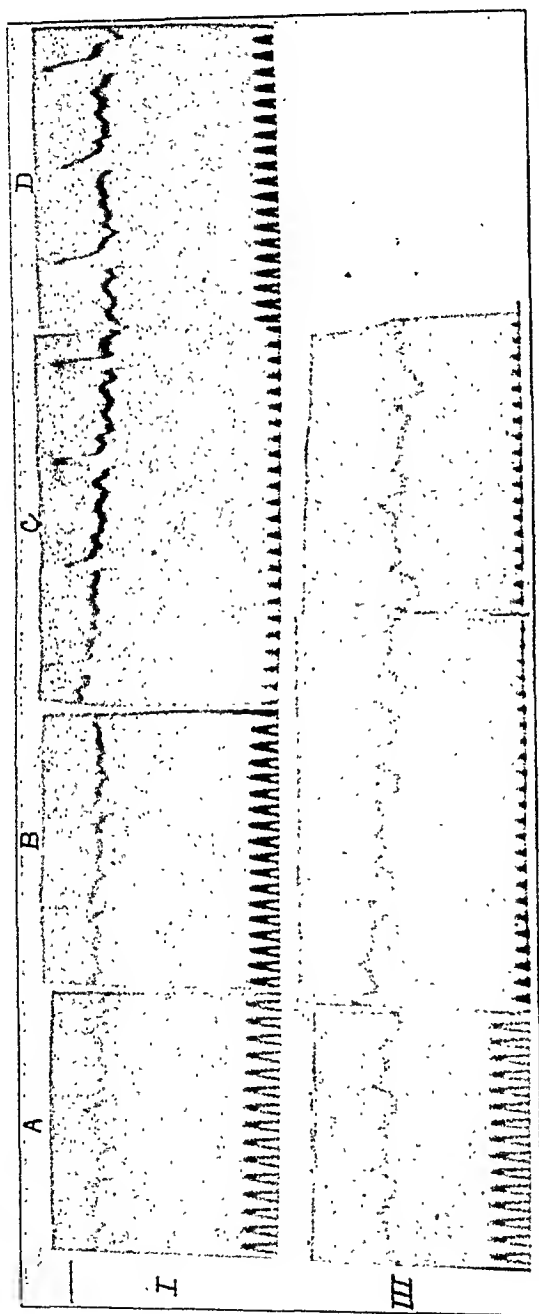


Fig. 2.—The effect of ligation of the descending branch of the left coronary artery in the heart-lung preparation. *A*, Leads I and III taken at the time of ligation; *B*, taken forty seconds after ligation; *C*, seventy seconds after ligation, and *D*, ninety seconds after ligation. A slight elevation of the S-T segment in Lead I and depression of the segment in Lead III. Inversion of the P-wave within forty seconds was noted. Increase in the QRS duration began at eighty seconds and continued until one hundred twenty seconds when the heart passed into complete heart-block. The T-wave inverted in Lead III.

The switching over of the coronary blood supply from normal to the perfusion reservoir did not bring about any change in the electrocardiogram whatever. In several experiments the right and left coronary arteries were supplied from two different reservoirs so that asphyxial blood

could be introduced in one of the arteries while the other continued to be perfused with normal blood.

Perfusion of the left coronary artery with asphyxial blood produced an inversion of the T-wave in Lead III and a high upright T-wave in Lead I. The R-T interval was elevated in Lead I and depressed in Lead III.

Perfusion of the right coronary artery with asphyxial blood produced an inversion of the T-wave in Lead I and an elevation of it in Leads II and III. The R-T interval was depressed in Lead I and elevated in Lead III. The side of the heart which was perfused with asphyxial blood showed unmistakable signs of dilatation, and, if the perfusion was prolonged, ventricular fibrillation took place.

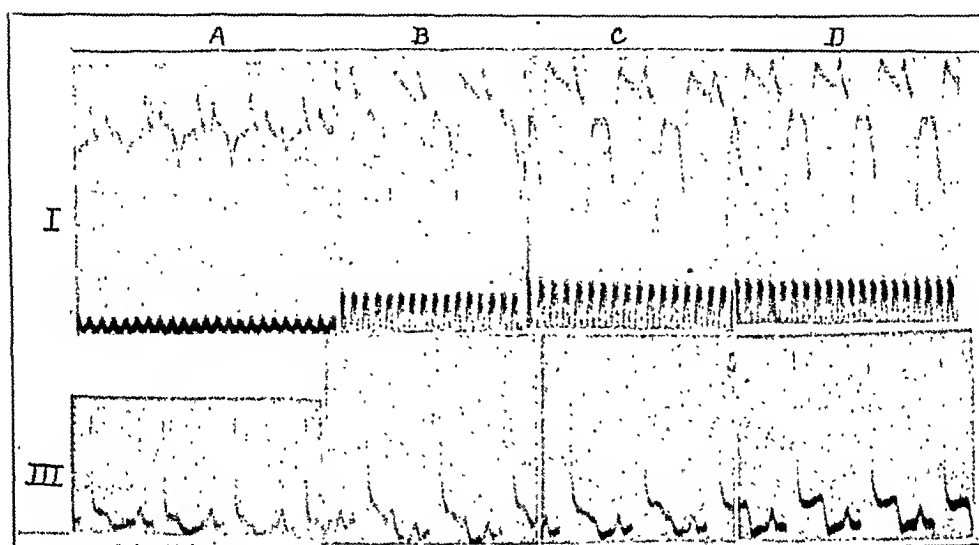


Fig. 3.—The effect on the electrocardiogram of perfusion of the right coronary artery with asphyxial blood. A, two minutes after perfusion began; B, three minutes; C, four minutes; D, five minutes. When the left coronary artery was perfused, the opposite change occurred, elevation of the R-T segment in Lead I and depression of S-T segment in Lead III.

In order to determine whether anoxemia was the sole operative factor in producing these changes, the coronary blood vessels were perfused with blood containing potassium cyanide in concentration of 1.0 millimol. Perfusion of either of the coronary blood vessels with cyanide blood did not produce changes in the electrocardiogram which were comparable with those resulting from perfusing with asphyxial blood. A decrease in size and an inversion of the T-waves in all leads was noted. In some experiments the perfusion with cyanide blood was carried until the point of prefibrillation was reached, but no definite changes in the R-T interval could be detected.

Oxygenated blood containing 80 vol. per cent of carbon dioxide (P_H 7) was perfused through the coronary blood vessels. No change in the R-T interval took place, and the T-wave became conspicuous. There was noted a development of ventricular extrasystoles arising on the per-

fused side; they usually developed soon after the perfusion with CO_2 rich blood was started and continued until fresh blood was readministered.

The results of the experiments described in this communication show that anoxemia and excess of CO_2 acting on the heart separately fail to reproduce the electrocardiographic change seen in coronary asphyxia. At the present state of our knowledge it is impossible to advance any

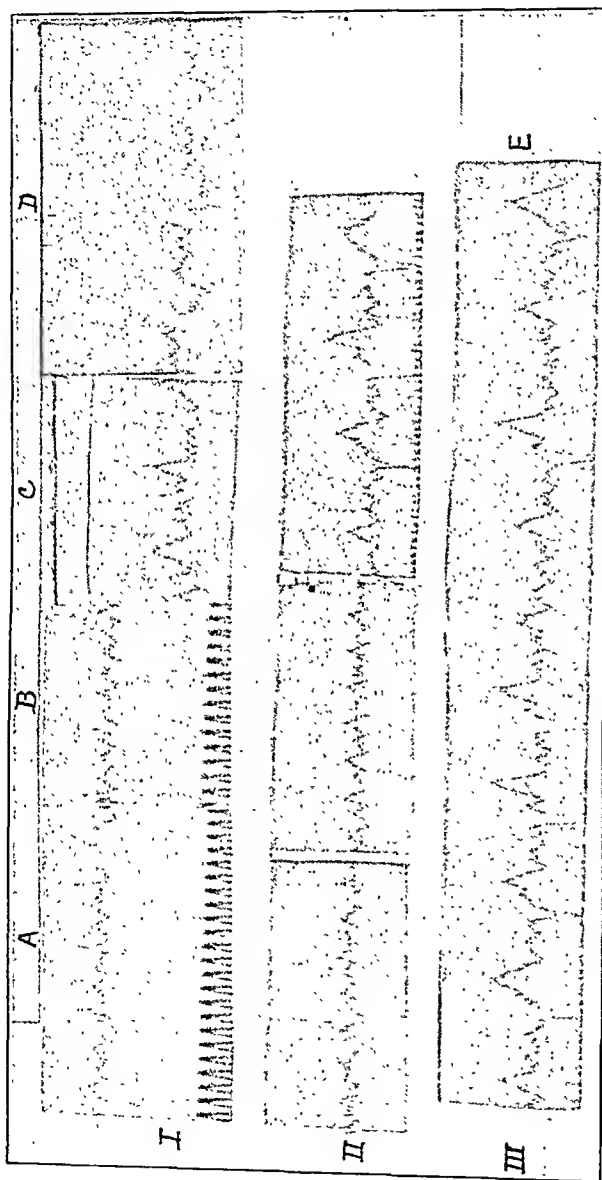


Fig. 4.—Arterial blood substituted with 80 vol. per cent carbon dioxide substituted for normal blood perfused through the left coronary artery. A, Leads I and III before perfusion; B, Leads I and III thirty and forty seconds later; C, Leads I and III ninety and one hundred ten seconds after perfusion began; D, one hundred thirty to one hundred forty-five seconds; and E, Lead III one hundred sixty seconds after perfusion began. A marked increase in size of T-wave in Lead III with but little change in the R-T segment. Many runs of ventricular extrasystoles were noted.

definite suggestion in regard to the real cause of the changes in the R-T interval observed during asphyxia. It is possible that the additive action of anoxemia with excess of CO_2 may account for the electrocardiographic change.⁹ It is, however, also possible that the change is due to some third factor such as an accumulation of metabolites in the tissue. Although perfusion of the heart with anoxemic blood would lead to the

production of these metabolites, it would prevent their accumulation on account of being washed off with the blood supplying the capillaries. Increase of CO_2 in the blood would lead to an increased CO_2 tension in the tissues, but on account of the oxygen still being present a large accumulation especially of abnormal products of oxidation would not take place.¹⁰ In coronary occlusion, however, these metabolites would be produced and not washed out of the tissue. Just as in the case of administration of blood removed from an asphyxiated animal of another heart lung preparation, the metabolites in addition to those produced by the heart would be administered to the heart muscle from external sources.

SUMMARY

Perfusion of coronary arteries of the dog with asphyxial blood produces changes in the electrocardiogram similar to but more marked than those produced by clamping the coronary arteries. These changes in the electrocardiogram are found to be comparable to those observed in coronary diseases in the human heart. Neither anoxemia nor excess of CO_2 separately produces the changes observed in asphyxia. Administration of cyanide, producing the severest form of anoxemia, also fails to produce these changes.

It is suggested that the change in the R-T segment typical of experimental asphyxia of the heart and probably of human coronary disease is due to a high concentration of locally produced metabolites. Perfusion with anoxemic blood tends to lower or invert the T-waves of the electrocardiogram in different leads depending upon which ventricle is affected. Excess of CO_2 increases the size of the T-wave in all leads and causes a development of ventricular foci.¹⁰

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PAROXYSMAL HYPERTENSION ASSOCIATED WITH A GANGLI- ONEUROMA OF THE SUPRARENAL MEDULLA*

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TUMORS of the suprarenal medulla have been noted in several cases in conjunction with paroxysmal hypertension, vasomotor and gastric disturbances, and other phenomena apparently dependent upon an autonomic imbalance. This association has suggested a definite clinical syndrome, with the tumor as the etiological factor. Suprarenal medullary tumors have been classified by Oppenheimer and Fishberg¹ as: sympathoblastomas, composed of immature sympathoblasts; gangli-
oneuromas, composed of relatively mature sympathetic ganglion cells; and paragangliomas, composed of apparently mature chromaffin cells. It has usually been in association with these latter tumors that paroxysmal hypertension has been recorded. Cases have been described as follows:

Labbé, Tinel and Doumer²: A woman of twenty-eight years suffered from attacks initiated by malaise, pallor and coldness and extreme vasoconstriction of the extremities. Next occurred a sensation of epigastric constriction, with nausea and vomiting, followed by palpitation and increased heart rate. The attacks terminated with extreme vasodilatation and profuse sweating, leaving the patient exhausted. Between attacks the blood pressure was 15 systolic, 10 diastolic (Pachon sphygmomanometer). During attacks it rose to systolic 26-28, diastolic 16-19, in other words, to nearly double the ordinary pressure. Death occurred during an attack of pulmonary edema. Autopsy revealed a paraganglioma as the only significant finding.

Labbé, Azérad and Violle³: A man of twenty-nine years for ten years had attacks similar to those of the previous case, associated with similar paroxysms of hypertension. A right hemiplegia resulted from one attack, and death occurred during another. Autopsy showed a paraganglioma of the suprarenal.

Oberling and Jung⁴: A woman of twenty-eight years, near the end of a second pregnancy, had severe headache and some albuminuria. The blood pressure showed considerable fluctuations, 250 mm. systolic and 190 mm. diastolic to 170 mm. systolic and 110 mm. diastolic. The delivery was normal, but the patient died shortly after in shock. At postmortem examination a paraganglioma of the left suprarenal was found.

Rabin⁵: A man of forty-five years for many years had hypertension and nervous manifestations similar to those of exophthalmic goiter.

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The blood pressure was variable, from 226 mm. systolic and 108 mm. diastolic to 177 mm. systolic and 122 mm. diastolic. After a week of fever, he developed signs of meningitis, and died, with a clinical diagnosis of Grave's disease with chronic nephritis and hypertension. Autopsy showed normal thyroid and kidneys; generalized arteriosclerosis; cardiac hypertrophy; chronic passive congestion of the viscera; lung infarcts. There was a pheochromocytoma of the right suprarenal medulla, with areas of necrosis and hemorrhage and venous thrombi. Although definite paroxysms of hypertension with marked vasomotor disturbances were not noted, the marked variations in blood pressure with the evidences of autonomic imbalance are suggestive.

Vaquez, Donzelot and Geraudel^{6, 7}; Laubry⁸: A man of thirty-seven years suffered from attacks of severe abdominal and thoracic pain; marked vasomotor disturbances and paroxysms of hypertension. He was treated with radiotherapy to the lumbar region. The attacks disappeared, to recur six months later and to disappear again, following further irradiation. They again recurred, and the patient died suddenly in a condition resembling that of uremic coma. Autopsy revealed a paraganglioma of the right suprarenal. The kidneys and other organs were normal.

Shipley⁹: A woman of twenty-six years had attacks consisting of precordial pain, palpitation, headache, nausea, vomiting, diarrhea, vasomotor phenomena and paroxysms of hypertension. She was operated upon, with removal of a paraganglioma of the right suprarenal. There was considerable shock attendant upon this operation, but the patient recovered uneventfully, and ten months later was still entirely free from attacks.

Mayo¹⁰: A woman of thirty years had attacks of dyspnea, palpitation, thoracic and abdominal pain, headache, pallor, and numbness and coldness of the extremities. During attacks the blood pressure rose from 130 mm. systolic and 82 mm. diastolic to 300 mm. systolic and 180 mm. diastolic. At operation a tumor, which appeared to be an enormous sympathetic ganglion, was found behind the tail of the pancreas, and removed. Microscopically, it somewhat resembled a suprarenal cortical adenoma, but was not characteristic and was finally diagnosed as a retroperitoneal malignant blastoma. Following the operation there was immediate, complete and permanent relief of symptoms, and the systolic blood pressure was never found to exceed 120 mm.

Porter and Porter¹¹: A man thirty-nine years old had had attacks, precipitated especially by lying on the left side, of nausea and ashen pallor, during which the blood pressure rose from a systolic of 110 to more than 200 mm. in 90 seconds. At operation an alveolar carcinoma of the adrenal cortex was found. The operation was followed by profound shock, but the patient made a complete recovery; there

was no recurrence of the attacks, and he could lie on the left side without discomfort.

In six of the above eight cases a tumor of the suprarenal medulla was demonstrated at autopsy or at operation. In this connection Rabin's conclusions, drawn from a series⁵ of 30 cases of such tumors, are of considerable interest: The tumor is a neoplastic growth, benign, encapsulated, nonmetastatic, which has a cellular structure similar to that of the normal suprarenal medulla. It appears to be actively secretory; the chromaffin reaction evidences a strong reducing substance probably epinephrine. Epinephrine was always present when qualitative tests were made. Quantitatively, it was found in larger amounts than in the normal suprarenal. Other associated findings were: nine cases of hypertension independent of renal disease; arteriosclerosis found regularly in the cases associated with hypertension; glycosuria in four cases, in two of which the pancreas was proved normal at autopsy, in the other two of which its condition was not stated; many cases showing symptoms of vasomotor or sympathetic instability or severe shock incommensurate with its apparent cause; four cases of neurofibromatosis. Rabin points out that although epinephrin could cause many of these symptoms, yet increased absorption has never been proved, although the vascularity of the tumor is suggestive; proof of a casual relationship between the tumor and the clinical state requires the demonstration of a hyperadrenalinemia, which is not possible with present methods.

Vaquez, Donzelot and Geraudel⁷ point out that the explanation becomes more complicated in the case of a cortical tumor, which throws discredit on the theory of hyperadrenalinemia. They feel that this argument becomes less important if one considers there is grave doubt as to the embryological and physiological duality of the suprarenal parenchyma.

In explanation of the gastric symptoms, Labbé, Tinel and Doumer suggest either mechanical irritation by the tumor or more probably a local vasoconstrictive crisis associated with the peripheral vasoconstriction.

REPORT OF CASE

Patient L. Z., male, aged forty-six years, an Italian furrier, was admitted to the First Medical Division of the New York Hospital on Nov. 6, 1930.

The family history and past history were not significant.

For nine years the patient had been subject to attacks of nausea, vomiting, numbness, dizziness and pallor, followed by flushing and profuse sweating. During the past two or three years the following other conditions had arisen: (1) Several sore throats diagnosed as tonsillitis. (2) Slight cough and occasional hemoptysis. (The sputum was repeatedly negative for tubercle bacilli.) (3) Polydipsia, polyuria, nocturia, polyphagia and occasional intense itching. (4) Loss of twenty pounds in weight. (5) Loss of sexual power. (6) Palpitations, not related to effort.

Physical Examination.—The patient was a moderately well nourished man forty-six years old, with florid complexion and grayish white hair, who appeared older

than his given age. The significant findings included: (1) Enlargement of the heart to the left (12.5 cm.). Rate 90, rhythm regular. (2) There was a soft systolic murmur at the apex, and at the right of the sternum in the second intercostal space. (3) The arteries were markedly sclerotic. Ophthalmoscopic examination showed marked arteriosclerosis and endarteritis, haziness of the discs, scars of old hemorrhages and several fresh hemorrhages. (4) The blood pressure on admission was 160 mm. systolic, 120 mm. diastolic. (5) The liver edge was palpable below the right costal margin. (6) A mass in the left upper quadrant, thought to be spleen, was palpable on deep inspiration.

Detailed Account of Attacks.—Sometimes precipitated by turning or bending, at other times without discernible cause, the attacks would grip the patient with startling suddenness. At the onset the patient would become weak and dizzy, and complain of numbness of the extremities; his usual florid coloring would change completely to one of marked pallor, and the extremities would become cold and have a mottled appearance. Soon there would be a feeling of nausea frequently followed by vomiting. Later, with relief of the subjective sensations, the patient would become very flushed and a profuse diaphoresis would occur, such as to drench the clothing and bed. Marked fluctuations in blood pressure accompanied these symptoms, for example, immediately after the onset of one attack, the blood pressure was found to be 280 mm. systolic and 180 mm. diastolic. The patient complained of numbness, weakness and nausea. He denied pain, headache or visual disturbance. He was pale and the extremities were cold and had a mottled purplish appearance. There was a moderate tremor of the hands. The apex beat was forcible, the rate 100, regular in rhythm. Ten minutes later the blood pressure was 250 mm. systolic and 150 mm. diastolic. There was marked subjective improvement, the color became flushed and there was a diaphoresis. The pulse was 90, regular in time, but alternate beats felt strong and weak. Thirty minutes after the onset the blood pressure was 130 mm. systolic and 98 mm. diastolic. The pulse rate was 100. Fifteen minutes later a similar attack occurred, the blood pressure reaching 270 mm. systolic and 180 mm. diastolic. It fell in twenty minutes to 118 mm. systolic and 90 mm. diastolic.

At times the attacks assumed a milder form, consisting of either vasomotor or gastric disturbances alone, or of any combination of the two. They occurred frequently, sometimes several times a day. As stated above, the only causative factor which the patient had noticed in this connection was change in position, and for years he had been afraid to lie on his left side lest this should precipitate an attack.

Laboratory Findings.—Blood count: red cells 4,750,000, hemoglobin 65 per cent, white cells 11,600, polynuclears 75 per cent, lymphocytes 25 per cent. Urine: cloud of albumin, sugar four plus, no acetone. Blood sugar 375 mg. per 100 c.c. Blood urea nitrogen 13 mg. per 100 c.c. Blood Wassermann reaction negative. Sputum negative on three occasions for tubercle bacilli. X-ray films of lungs showed no evidence of pulmonary disease but did show what was apparently a muscular weakness of the left diaphragm, confirmed by fluoroscopy, and suggestive of an early eventration. Fluoroscopy of stomach showed a narrowed appearance of the antrum. There was a large indefinite mass on the left, thought possibly to be spleen. Basal metabolic rate 23 per cent above average normal. Red test for kidney function: 35 per cent excretion of the dye two hours after intramuscular injection. Pulse rate 70-100. Successive electrocardiograms on various occasions showed many variations: Normal sinus rhythm; premature auricular beats; inversion of T-wave of coronary type in the first two leads; no inversion; left axis deviation of QRS; no axis deviation of QRS.

Course.—The patient was given a diabetic diet and insulin. It was found rather difficult at times to differentiate a mild attack of the patient's usual type from mild insulin shock. Before discharge there was occasionally one or two plus sugar in the

early morning specimen. The others were negative. The blood sugar was 180 mg. on discharge. The diet was carbohydrate 140 gm., protein 80 gm., fat 70 gm. Insulin 62 units a day. During the patient's stay the attacks diminished in frequency and intensity, but were still troublesome. He was discharged Dec. 6, 1930.

Because the patient's clinical syndrome of vasomotor and gastric disturbances, associated with signs of instability of the vegetative nervous system, especially the paroxysmal hypertension, so closely resembled the syndrome associated with cases of suprarenal tumor as described in the literature, it was believed that the patient was suffering from this condition. The exact etiology of the hyperglycemia and glycosuria could not be determined. The possibilities were considered of an independent diabetes; of a sclerosis of the pancreas associated with the marked arteriosclerosis found elsewhere; of a hyperglycemia dependent upon a hyperadrenalinemia. On the basis of a diagnosis of adrenal tumor the advisability was considered of surgical removal of the tumor, as was done successfully in the cases cited above. However, it was felt that the patient's general condition was not good enough to warrant operative interference. Such cases are at best subject to severe shock from even minor operative procedures, and the present case was complicated by the diabetic condition and the marked arteriosclerosis. As Laubry obtained considerable relief in a similar case by irradiation of the adrenal region, it was decided to use x-ray treatment in the present case, after which, if improvement occurred, surgery might be reconsidered.

Under the supervision of Dr. John R. Carty x-ray treatment was given as follows: "Medium wave aluminum filtered radiation at 130 K.V.P. applied posteriorly over the suprarenal region on each side. Each area received four treatments from Feb. 11, 1931, to April 22, 1931, averaging approximately three-quarters of a skin erythema dose at each treatment. Slight improvement was noted following the last treatment; subsequently the patient went downhill."

The attacks continued during the treatment. Following the development of an infection of the hand and a corneal ulcer, hospitalization was advised, but declined, as the patient felt he must try to continue work. He could not follow dietary directions, so continued to have glycosuria, polydipsia and polyuria. July 12, 1931, he re-entered the hospital in a moribund condition. There was congestive heart failure with dyspnea, orthopnea, vomiting, pulmonary congestion, pleural effusion and edema. He died within two hours of admission.

Autopsy Findings.—Heart: hypertrophied, weighing 600 gm. Aorta: marked atheroma. Lungs: congested. Bilateral pleural effusion. Stomach: dilated with four liters of dirty yellow fluid. Liver: congested. Spleen: thickening of arterial and arteriolar walls. Pancreas: normal except slight increase in fibrous tissue and thickening of the walls of the smaller arteries. The islands of Langerhans were well marked and normal in appearance. Kidneys: the cortex was somewhat reduced on section, and microscopically there were changes compatible with mild chronic vascular nephritis. Right adrenal: normal.

A tumor, the size of a large grapefruit, was found retroperitoneally in the left upper quadrant, displacing the kidney downward and the left dome of the diaphragm upward. The tumor derived its blood supply from the abdominal aorta, above the left renal artery. It was attached by a pedicle to the midline structures. In removing it a portion of what was apparently the left adrenal was found in the adjacent tissues, but its exact relation to the tumor could not be demonstrated. The smooth surface of the tumor was covered with dilated veins, and there was a thick fibrous capsule. There were a few cysts just inside the capsule and the center of the mass was necrotic. Microscopically, the tumor was composed of masses of cells having a rather striking resemblance to those of the suprarenal medulla. The cells were large, irregular, with bluish staining cytoplasm which strung out into fibrils. The large ovoid nuclei had prominent nucleoli. The cells were arranged loosely in

lobes and lobules with dense fibrous capsules. Their resemblance to nerve tissue ganglionic cells would seem to point to ganglioneuroma, originating in the adrenal medulla, as the most probable diagnosis. A stain for chromaffinity was negative.

The left adrenal was found among the tissues adjacent to the tumor as previously described. Microscopically, it showed normal cortical and medullary cells, but near its torn edge appeared a heaping up of the medullary cells to form an abnormal looking nodule surrounded by thinned-out cortex. In the light of the resemblance of these cells to those of the tumor this hyperplasia would seem significant.

SUMMARY

1. A review has been given of several cases of suprarenal medullary tumors, one cortical tumor and one retroperitoneal malignant blastoma, somewhat resembling a suprarenal tumor, which were associated with paroxysmal hypertension, gastric disturbances, and various symptoms of imbalance of the vegetative nervous system.

2. A report has been given of a case of ganglioneuroma of the suprarenal medulla associated with evidences of imbalance of the vegetative nervous system: (a) vasomotor phenomena, notably paroxysms of hypertension, followed by profuse sweating; (b) disturbance of the carbohydrate metabolism in the absence of a pancreatic lesion; (c) elevation of the basal metabolic rate; (d) gastric disturbances.

3. Treatment: Medical treatment has universally been reported as ineffectual. X-ray therapy was palliative but not curative in the case of Vaquez^{6, 7} and Laubry.⁸ In the present case it was only slightly palliative. Surgical removal of the tumor has produced a cure in three cases and seems the most promising mode of treatment.

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AN AMPLIFIER FOR HEART SOUNDS OPERATING ON ALTERNATING CURRENT*

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VACUUM tube amplifiers for heart sounds employing either multiple headphones or a loud-speaker, have been described by many workers during the past decade. In this country interest in the amplification and registration of heart sounds was stimulated by the work of Williams¹ and Squier, reported by Winters,² in 1921. Within the next five years Cabot,³ Cabot and Dodge,⁴ Frederick and Dodge,⁵ Gamble,⁶ and Gamble and Replogle⁷ contributed valuable work in this field. More recently Waud⁸ has described an easily constructed amplifier which enables a number of persons to listen to greatly amplified heart sounds or murmurs. In Europe even more extensive work has been done with amplifiers of body sounds. In Germany, Bass,⁹ Trendelenburg,¹⁰ Scheminzy,¹¹ Pierach,¹² Landes,¹³ Schwarz¹⁴ and others have reported excellent work. Duchosal¹⁵ and Duchosal and Mozer¹⁶ have done outstanding work in Switzerland.

Most of the amplifiers that have been devised are bulky and hardly portable. This has been true largely because of the fact that they are energized by direct current, necessitating the use of batteries. In this paper the authors wish to describe an amplifier which operates on the ordinary alternating current supply and for which no accessory batteries are required. Furthermore, the outfit is constructed entirely of parts which may be obtained from any radio supply house. It can be built by anyone at all handy with tools for a cost of not over thirty-five dollars.

The entire amplifier and loud-speaker are housed in a sturdy box of the type designed for portable radio sets. This case measures 18 by 11 by 10 inches and is procurable at radio supply houses. Fig. 1 shows the amplifier with the front piece which protects the control knobs removed. A switch for the alternating current supply is seen near the middle of the panel. Below it is the potentiometer input control. To the left are four jacks, one for the input and three for headphones in the output circuit. The control at the extreme left regulates the volume in the headphones.

A modification of the well known Loftin-White direct coupled amplifier is used. Examination of the circuit diagram (Fig. 2) shows that in addition to the usual screen grid tube directly coupled to a power amplifier an additional screen grid tube is employed. This tube is

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resistance-coupled to the others and adds materially to the sensitivity of the outfit. The constants of the resistances and condensers needed are also shown in the figure. It should be pointed out that the resistance R 9 which must have a value of 4300 ohms is obtained by using the field of the dynamic speaker and a suitable resistance either in parallel or in series with it, so that the total resistance of the combination will have the desired value. The speaker that was employed in our unit has a field resistance of 5000 ohms. To bring the resistance down to

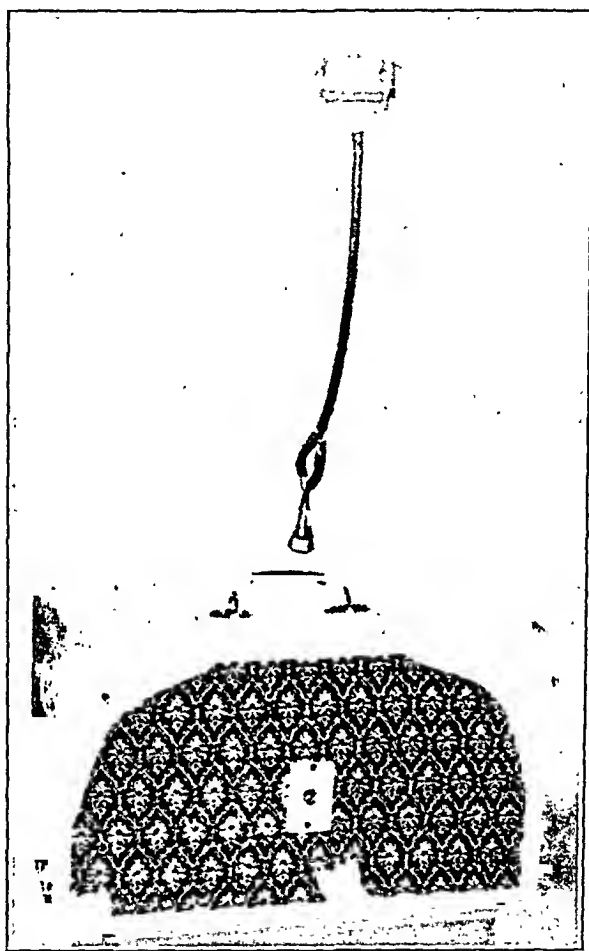


Fig. 1.

4300 ohms it was necessary to shunt the field with a resistance of about 30,000 ohms.

The chief difficulty encountered in the construction of the amplifier operating on alternating current is the elimination of the sixty cycle hum. The operation of our amplifier is quite satisfactory in this respect. The alternating current hum is scarcely audible in the loud-speaker and even with the headphones it is not objectionable until the volume is greatly increased. The large capacity of the filter condensers C 5 and C 6 and the careful grounding of the circuit at all points indicated are important factors in the elimination of alternating current hum.

An amplifier of the type described has an excellent fidelity curve. In other words, it amplifies without distortion over a wide frequency range. The results obtained with even the best of amplifiers, however, are not good unless a microphone with an equally good frequency response is employed. Microphones of the carbon, electromagnetic and condenser

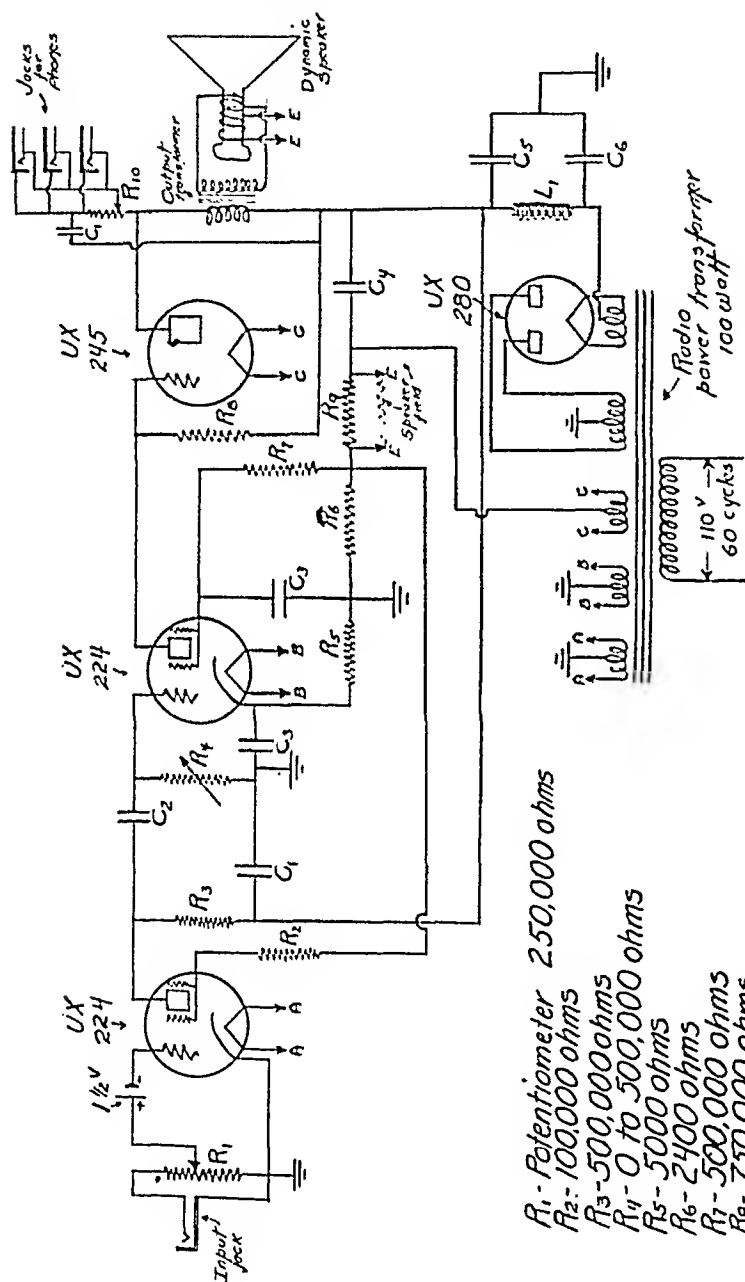


Fig. 2.

- R_1 - Potentiometer 250,000 ohms
 R_2 - 100,000 ohms
 R_3 - 500,000 ohms
 R_4 - 0 to 500,000 ohms
 R_5 - 5000 ohms
 R_6 - 2400 ohms
 R_7 - 500,000 ohms
 R_8 - 750,000 ohms
 R_9 - 4300 ohms
 R_{10} - Potentiometer - 30,000 ohms
 C_1 - 1 microfarad
 C_2 - 0.01 " "
 C_3 - 2.0 " "
 C_4 - 3.0 " "
 C_5 - 12.0 " " (electrolytic)
 C_6 - 8.0 " "
 L_1 - 30 henry choke

types were tried, but the latter was by far the most satisfactory. Carbon microphones, although they are very sensitive and have a fairly good frequency response, are noisy. Several types of electromagnetic units were tried but none was found which gave good quality and was at the same time sufficiently sensitive. The condenser microphone responds

equally to sounds varying from 30 up to several thousand cycles per second, and, as Cabot and Dodge⁴ have shown, practically all cardiac sounds fall within this range. In addition to its excellent fidelity the condenser microphone is very sensitive. Unfortunately this microphone is not only the most expensive of the three types, but it requires the use of an additional tube amplifier which employs a direct current supply.

In using the condenser microphone it was found that if the instrument was placed directly on the chest wall many murmurs were very poorly reproduced. Apparently this was due to damping effects within the closed microphone chamber. At any rate the difficulty was obviated by connecting the microphone to a short piece of rubber tubing ending in an ordinary stethoscope bell. Fig. 1 shows the microphone and tubing arrangement suspended above the amplifier.

The rubber tubing employed was about eighteen inches long and had an inside diameter of about one-quarter inch. It was fastened to the microphone by means of a glass connector which fitted snugly into a thin cork disk of large diameter. The cork was firmly held to a sponge rubber ring (which had been glued to the microphone chamber) by means of rubber bands. At the other end of the tube different types of stethoscope bells were attached, as shown in Fig. 1. The volume of the amplified sounds was reduced materially when compared with the volume obtained with the microphone directly on the chest wall. Further investigation of the acoustic properties of the sound conducting system and various types of stethoscope attachments is in progress.

It should be mentioned that, when any amplifier having a loud-speaker is used, precautions may be necessary to eliminate "feed-back" from the speaker to the microphone. This feed-back causes howling and renders satisfactory operation impossible. With an extremely sensitive amplifier and microphone, such as we have described, complete removal of the feed-back is surprisingly difficult. The remedy quite obviously consists in preventing extraneous noise from entering the microphone. This may be accomplished by careful shielding of the microphone or by increasing the distance between amplifier and microphone until howling no longer occurs.

It should be emphasized, perhaps, that, although the amplifier (except for the single cell-1½ volt grid bias) operates entirely on alternating current, when the condenser microphone is used, batteries to supply the accessory vacuum tube are required. It is possible that further studies may enable us to use an alternating current supply for the microphone also.

When the condenser microphone is used with the amplifier, the volume of the amplified sounds is sufficient to enable them to be heard in a large room, and we believe that the instrument should be of considerable value for teaching purposes. While amplifiers that employ

multiple headphones have the advantage that the sounds come to the ear through rubber tubing and are consequently similar to sounds heard through a stethoscope, nevertheless an amplifier employing a loud-speaker is in many ways more practicable for use in teaching.

SUMMARY

A sensitive audio-frequency amplifier with a loud-speaker operating on alternating current and suitable for the amplification of heart sounds and murmurs is described. The condenser microphone has been found to be superior to other microphones for use with the amplifier.

The authors wish to acknowledge their indebtedness to Professor L. N. Holland of the Electrical Engineering Department of the University for his kindness in loaning the condenser microphone and for his helpful suggestions. We also wish to express to Dr. Frank N. Wilson our appreciation for his interest and assistance which have been invaluable in the completion of this work.

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Department of Clinical Reports

CONGENITAL HEART DISEASE

COR BILOCULARE*

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THE extreme rarity of pure biloculate hearts warrants the report of a single case. Abbott¹ in her statistical study of 1,000 congenital hearts analyzed only nine cases of this anomaly. The x-ray and anatomical findings of the case to be described are as instructive as they are unusual.

CASE REPORT

A. B., male, aged four months, admitted January 26, 1932, died January 26, 1932.

Chief Complaint: Dyspnea. *Family History:* Negative. *Past History:* The child had been a "blue baby" since birth and had gained weight very slowly. He became dyspneic on the day of admission and began to foam at the mouth. The child was in *extremis* when brought to the hospital. *Physical Examination:* A marantic infant, markedly cyanotic and gasping for breath. The heart was on the right side. There were no murmurs heard. The finger nails were curved, suggestive of clubbing. The liver was enlarged. The child was placed in an oxygen tent, given stimulation, but expired an hour and a half after admission.

Röntgen Examination: An examination of the chest showed the heart to be almost entirely on the right side. It was markedly enlarged, reaching the axillary line on the right. It was globular in shape, with an irregularity on its upper right margin. (Fig. 1.) The appearance was that of a congenital heart with dextrocardia. There was only one large vessel arising from the base of the heart. This ran upward and descended to the right, disappearing in the shadow of the vertebral column.

Postmortem Examination: (Performed by Dr. E. B. Greenspan and Dr. S. Klein.) The body was that of a fairly well developed and well nourished infant of four months. There was no rigor mortis. There was marked acrocyanosis. The fontanelles were open and depressed. Both testicles were descended. *Neck:* There was a large superficial hematoma in the left side of the neck, the result of an attempt at phlebotomy. *Abdomen:* No free fluid present. The intestines, below the duodeno-jejunal junction, were in their normal position. The liver extended two finger-breadths below the costal margin and was seen to extend across the entire width of the abdomen. *Chest:* Both diaphragmatic leaves reached the sixth rib. No free fluid in either pleural cavity. *Thymus:* Normal in size, position and appearance. *Lungs:* The lungs were divided into supernumerary lobes, as follows: The right lower lobe was divided by incomplete fissures into three lobes; the right middle lobe, into two lobes; the right upper lobe, into three lobes; the left lower lobe, into three lobes. There was a left middle lobe which was divided into two portions by a deep fissure. The left upper lobe consisted of only one lobe. The pleura was smooth

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and glistening. The surface of the lungs, for the most part, was pinkish red with dark blue lobular markings. Several of the small lobes, especially those located posteriorly, were firm, dark blue and did not crepitate. The remainder of the lungs was only fairly well aerated. *Gastrointestinal Tract:* The esophagus was located on the right side of the vertebral column and appeared grossly normal. The lower end of the esophagus passed through the right crux of the diaphragm. The greater curvature of the stomach was on the right, the lesser curvature reached the



Fig. 1.—Roentgen-ray appearance of chest showing congenital heart with dextrocardia and single large arterial trunk.

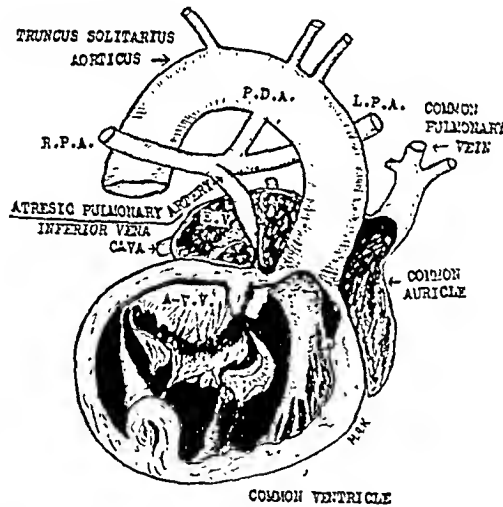


Fig. 2.—Semidiagrammatic sketch of specimen showing cor biloculare, situs inversus cordis, pulmonary artery atresia, truncus solitarius aorticus, patent ductus arteriosus (P. D. A.), common auricle, common auriculoventricular ostium with four auriculoventricular cusps (A-V. V.), Eustachian valve (E. V.), right pulmonary artery (R. P. A.), left pulmonary artery (L. P. A.).

midline and a fine filmy gastrohepatic omentum extended to the right lobe of the liver from the lesser curvature. The duodenum was situated mostly in the left lower portion of the right upper quadrant and hung from a double mesentery, the base of which attached to the upper and lower borders respectively of the neck and body of the pancreas. The stomach appeared normal. The duodenum was somewhat dilated and a little longer than normal, but showed no other changes. The remainder of the gastrointestinal tract was normal grossly. In the mesentery there were many pea- to almond-sized soft, pinkish gray lymph nodes which, on section,

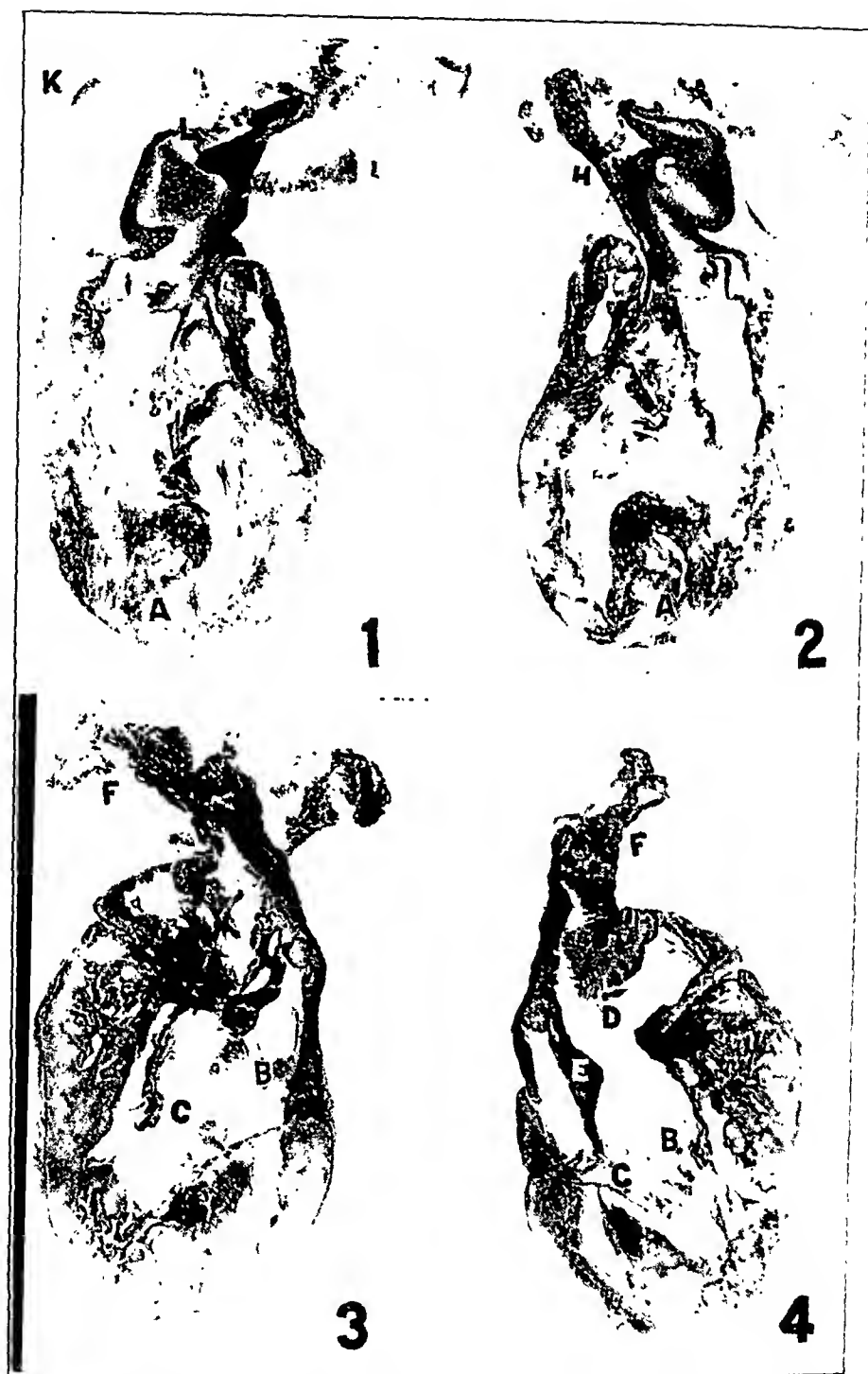


Fig. 3.—Coronal slabs cut through paraffinized heart. Anterior third (1), midportion, anterior view (2), midportion, posterior view (3), posterior third (4) of the heart showing common ventricle with rudimentary interventricular septum (A), common auriculoventricular ostium (B), with the four auriculoventricular cusps (C), common auricle (D) with hyperplastic eustachian valve (E), common pulmonary vein (F), truncus solitarius aorticus (G), atresic pulmonary artery (H), right and left branches of the pulmonary artery (K), patent ductus arteriosus (L).

presented many pinhead sized grayish nodules on a pink background. *Spleen*: The spleen and splenic vessels were not found after a careful search. In the greater omentum, extending from cardia to pylorus, and located just below and receiving branches from the gastropiploic arch, there was a lobulated soft, pink mass, about 1 cm. in width. *Liver*: The liver was enlarged to about one and a half times its normal size. It was in the normal position. The surface was smooth. Glisson's capsule was not thickened and its color was a uniform dark purplish red. The liver had a rubbery consistency and on cut section was pale brown, somewhat wet and presented a homogeneous surface. The gall bladder and duct system were normal. The gall bladder was attached to the right lobe of the liver. *Pancreas*: The pancreas was normal in size and consistency, but its position was abnormal. The head lay on the anterior surface of the second portion of the duodenum, the neck lay behind this portion of the duodenum, and the body and tail extended to the right. *Kidney*: The kidneys were slightly enlarged and the capsule stripped easily.

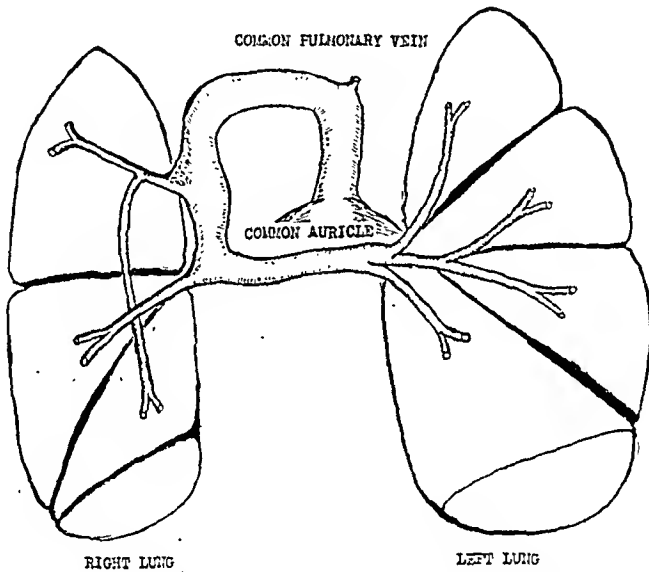


Fig. 4.—Anomalous venous circulation in the lungs.

Except for a marked congestion, they appeared normal. The ureters, bladder and prostate appeared normal. *Adrenal*: The adrenals were normal in size, shape and position. They were markedly congested.

Heart: The pericardial sac and contents were located entirely in the right chest. The long axis extended from left to right. There was no excess of pericardial fluid, and the pericardial lining was smooth and glistening.

The heart was enlarged and its apex was situated in the right part of the chest. A truncus solitarius aorticus arose from the bulbus cordis and coursed upwards and to the right over the right main bronchus, giving rise in its usual order to the innominate, carotid and subclavian arteries (Fig. 2). This vessel possessed three valve leaflets and two coronary artery orifices. The ductus arteriosus was patent and divided a short distance from its aortic origin into two branches, one going to the right and the other to the left lung. The pulmonary artery was atresic at its base. Its distal extremity became continuous with the branch of the ductus arteriosus which coursed to the right lung.

In order to preserve the topographic relations of the heart cavities, the organ was paraffinized according to the method of Gross and Leslie² and sectioned into three coronal slabs, i. e., anterior, midportion and posterior (Fig. 3). An examina-

tion of these slabs showed the heart to be two chambered. A common pulmonary vein entered into the left upper part of a common auricle. At the right and posterior part of this common auricle the superior and inferior vena cava entered and were separated from each other on the inner aspect of the auricle by a hyperplastic eustachian valve.

A common auriculoventricular ostium led into a single ventricular chamber. The walls of the auriculoventricular ostium bore four auriculoventricular cusps. The base of the ventricle had a small round elevation which represents the primitive interventricular septum. A muscular ridge arising from the base of the common ventricle and to the right of the primitive interventricular septum extended up the right lateral wall of the common ventricle to be inserted at the base of the aorta (Fig. 2).

The inferior vena cava was situated on the left side of the vertebral column. The aorta was smooth and elastic and was located in front and to the right of the inferior vena cava. The tributaries of the aorta were normal in position, except that the orifice of the celiac vessels was relatively narrow.

The venous circulation of the lungs also presented unusual anomalies (Fig. 4). The larger venous channels from all the lobes of the left lung united into one broad venous channel which crossed to the right and became continuous with a large venous sinus draining the right lung. This large venous channel continued cephalad and to the left to empty into the common auricle.

Anatomical Diagnosis:

1. Congenital heart disease.
 Cor biloculare (situs inversus cordis);
 Pulmonary artery atresia;
 Truncus solitarius aorticus (patent ductus arteriosus);
 Common auricle with absence of interauricular septum;
 Hyperplastic eustachian valve;
 Common pulmonary vein;
 Common auriculoventricular ostium with four auriculoventricular cusps;
2. Situs inversus of esophagus and stomach.
3. Supernumerary fissures and lobes of both lungs.
4. Anomalous rotation of pancreas and duodenum.
5. Congenital absence of spleen.
6. Pulmonary congestion, edema and atelectasis.
7. Congestion of viscera.

SUMMARY

The interesting features of this case, aside from its great rarity, are the presence of the four auriculoventricular valves which represent the primitive endocardial cushions, the hyperplastic eustachian valve, the common pulmonary vein and the unusual venous circulation of the lungs. An examination of the roentgenogram of the chest revealed only a single large artery going upward and descending to the right.

The author is indebted to Dr. Louis Gross and to Dr. Maude E. Abbott for their review of this case and to Dr. Bela Schiek for the use of the clinical data.

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VENTRICULAR TACHYCARDIA WITH ALTERNATING COMPLEXES*

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IN THE last ten years nineteen instances of bidirectional ventricular tachycardia have been described. Strass¹ in 1930 listed the reported cases, and since that time Clarke² has added another. Most of the cases were attributed to the action of digitalis. Some of them could scarcely

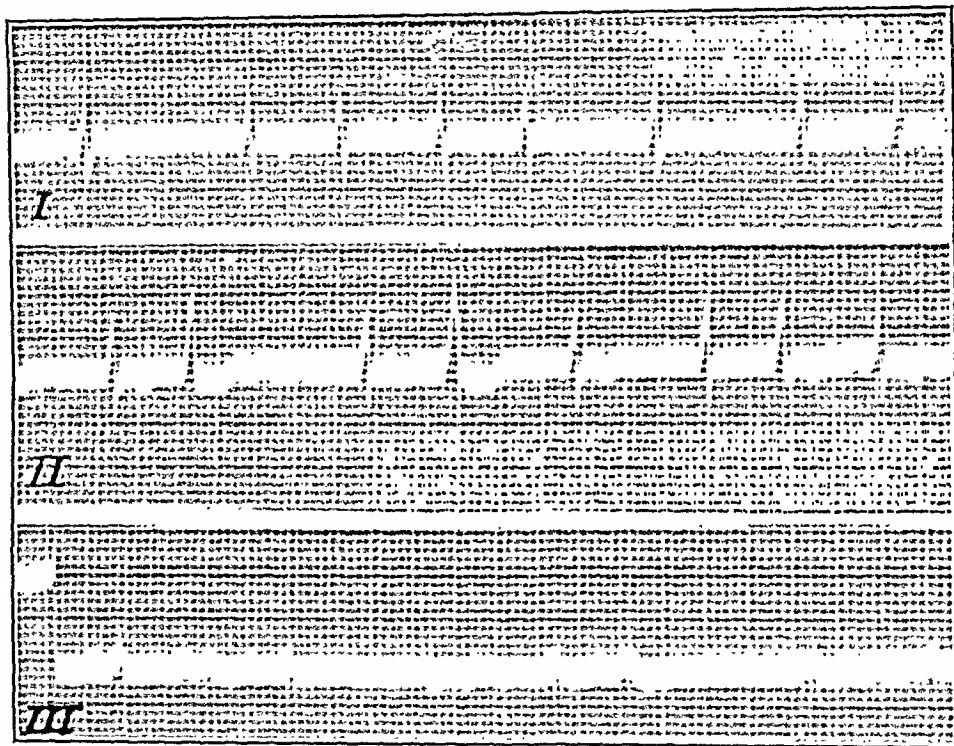


Fig. 1.—Tracing taken the day of admission, April 4, 1932, showing auricular fibrillation and occasional extrasystoles.

have been explained on this basis. There are probably other recorded cases buried in the literature under other titles. A case of this type, recently encountered in the Long Island College Hospital, presents some features which seem worthy of note.

CASE REPORT

M. L. (Hospital No. 2258) American born, a widower, a laborer by occupation, was admitted to the Long Island College Hospital, April 4, 1932, complaining of shortness of breath and swelling of the legs.

At the age of thirty years he had an attack of polyarthrititis lasting for two months. At thirty-six and thirty-eight years he had recurrences of the rheumatic fever lasting several months each time.

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After the third attack he began to notice dyspnea on effort, a tendency to cough, and a variable bluish tinge to the skin.

Two years before admission he coughed up about a cupful of blood, and was taken to a hospital, where he remained nine weeks. He tried to return to work once but was unable to continue because of increasing dyspnea and palpitation. Six months before admission he had another hemoptysis. Swelling of the ankles came on about one month before admission. He was admitted to another hospital at this time, and stayed about two weeks. For two years he had been taking digitalis tablets continuously, from one to four a day.

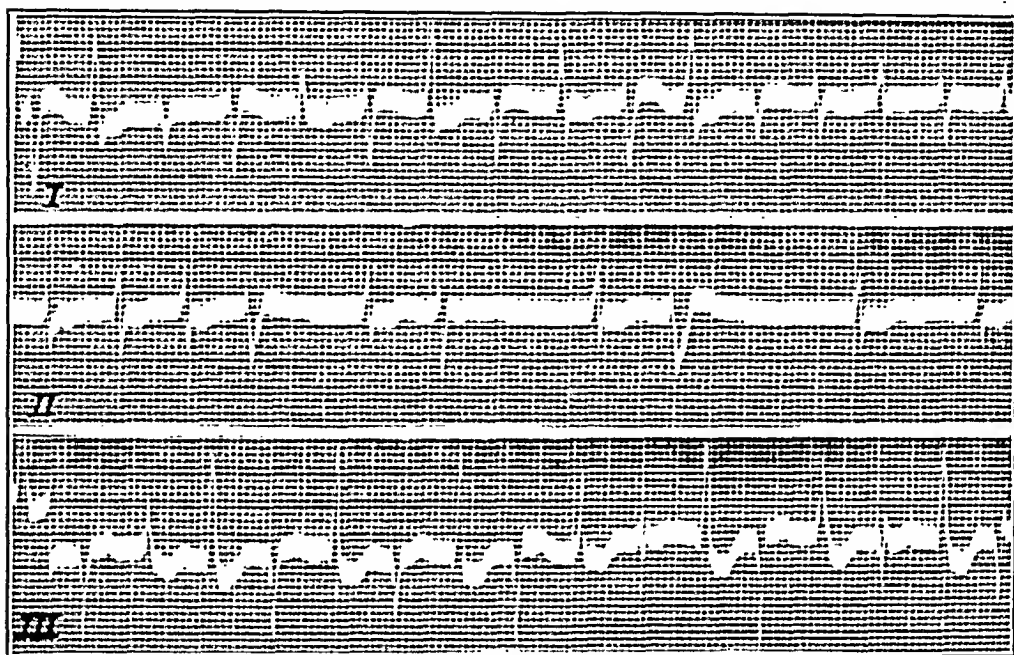


Fig. 2.—Bidirectional ventricular tachycardia. April 8, 1932. End of a paroxysm seen in Lead II. Twice in Lead I and once in Lead III the alternation reverses itself, as could scarcely happen were the mechanism one of bifocal pacemakers.

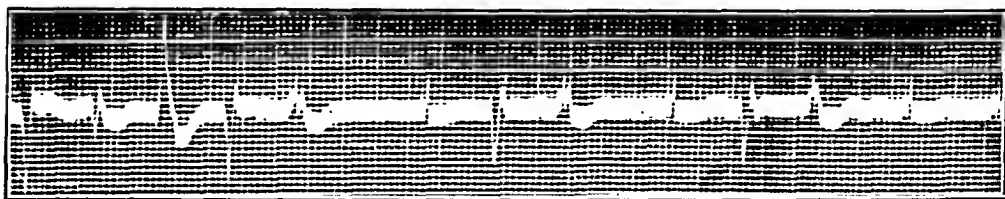


Fig. 3.—Lead III. April 9, 1932. End of a long paroxysm, followed by two paroxysms of three beats. Note the "normal" type of complex that occurs after each long pause, suggesting elapse of sufficient time for recovery of conductivity. (Cf. Robinson, G. C.: *Arch. Int. Med.* 18: 380, 1916.)

On examination: The temperature was 98.2°, pulse 120, respiration 42, blood pressure 100 mm. systolic, 75 mm. diastolic. He was orthopneic and cyanotic. The heart was enlarged, the borders being 5 cm. to the right and 12 cm. to the left of the midline. At the apex there was a rough systolic murmur and no second sound or diastolic murmur. No murmurs were heard at the base. The pulmonic second sound was accentuated. The rhythm was that of auricular fibrillation.

The lungs showed scattered musical râles and moist râles at the bases. The liver was enlarged and there was a dependent edema.

The day after admission the patient suffered a sudden pain in the right side

of the chest, followed by some hemoptysis and signs of an infarct. These gradually cleared up.

Course and Treatment: Digitalis was evidently indicated by the rapid heart rate in the presence of auricular fibrillation and congestive heart failure. It was known that he had been getting digitalis, but there was no way of telling how nearly digitalized he was. The electrocardiogram taken the day after admission (Fig. 1) showed only fibrillation with no clearly defined T-waves. It was decided to give him a one-grain tablet every four hours until the desired effect was obtained or toxic signs developed.

After four days he had received 1.66 gm. and his general condition had not changed very much. The heart rate was recorded as between 84 and 118. That morning the heart action was found to be alternating between a slow irregular arrhythmia and rapid regular periods lasting about thirty to sixty seconds. The electrocardiogram showed these phases to be auricular fibrillation interrupted by runs of bidirectional ventricular tachycardia (Fig. 2). After this was established graphically, it was noted that on listening at the apex during the runs of tachycardia, there was a distinct alternation in the loudness of the very regular systolic sounds.

The tachycardia was ascribed to overdigitalization, and the drug was immediately stopped. The runs of tachycardia recurred frequently for several days, and as they became less frequent there were short periods of bigeminy and trigeminy, with a gradually rising pulse rate, until after a period of seven days it was necessary to resume the drug in doses of one to two grains a day. He was subsequently discharged from the hospital, able to be up and about.

COMMENT

It is suggested that the mechanism of bidirectional tachycardia depends upon a relatively fixed delay in conduction time of one branch of the bundle, while the conductivity of the other branch waxes and wanes so that it alternately slightly exceeds and fails to equal that of the first branch.

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Department of Reviews and Abstracts

Selected Abstracts

Saphir, O.: Bands and Ridges in the Pulmonary Artery. *Arch. Path.* 14: 10, 1932.

The study here presented is based on the examination of bands in the pulmonary artery in one case and of ridges in the pulmonary artery in another case. Both structures were encountered in the course of postmortem examinations. The first case was a patient with arterial hypertension and nephrosclerosis of the arteriolar variety who died from cardiac decompensation. There were found many bandlike structures in the pulmonary artery in addition to arteriosclerotic plaques. Histologically the bands consisted of young and old connective tissue with hyalinization. There were endothelial cells and lymphocytes present, also many red blood cells and pigmented areas. Newly formed blood vessels and blood sinuses were found throughout. The bands themselves were lined by intimal lining cells and represented organized and still organizing thrombi. In the second patient who died from cardiac decompensation associated with diffuse arteriosclerosis, nephrosclerosis of the arteriolar variety and emphysema of the lungs, ridges were found in the pulmonary artery. Histological examination showed that these ridges were organized mural thrombi covered by intimal lining cells.

These structures are supposed to be the result of organized mural thrombi. It is believed that the systolic pressure in the pulmonary artery transformed the thrombi into bands. A congenital anomaly could be ruled out as the underlying cause of these structures. Pulmonary arteriosclerosis was the primary cause of the mural thrombi. There was no evidence of Ayerza's disease.

Katz, Louis N., and Ackerman, Walter: The Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles. *J. Clin. Investigation* 11: 1221, 1932.

Studies were made of the effect, in the open-chested anesthetized dog, of changing the heart's position on the electrocardiograms of induced extrasystoles. The shifts of the heart were (a) in an anteroposterior direction on the transverse axis at its base, (b) in a lateral direction on the anteroposterior axis at its base with practically no rotation on its long axis, and (c) rotation on its long axis (which runs from the base to apex) with some movement in a lateral direction on the anteroposterior axis at its base. The extrasystoles were induced in four regions, viz., the base and apex of the right and left ventricles.

The electrical axis of the various extrasystoles did not move the same amount nor always in the same direction when the heart was shifted. The electrical axis moved in the same direction as the anatomical axis in most types of beats when practically no rotation on the heart's own long axis accompanied the change in the heart's position. The electrical axis moved in a direction opposite to the anatomical axis in most types of beats when the heart was rotated on its own long axis at the same time.

Many times the direction of the major initial deflection of the extrasystoles was reversed in one or more leads.

The results are attributed to the unequal movements of the so-called three-dimensional vectors of the various extrasystoles when the heart was shifted. This resulted in an unequal and at times opposite movement of the projections of these three-dimensional vectors on the plane of the three leads.

The reversal in direction of the QRS group of ventricular extrasystoles, which often accompanied changes in the heart's position, shows (a) that the configuration and position of the heart cannot be ignored in analyzing the site of ventricular extrasystoles and bundle-branch block in man, and (b) that the direction of the QRS group of extrasystoles induced in the two patients reported with pericarditis and pericardial fistula may not be applied to the nondiseased human heart without consideration of the other factors involved.

On the basis of these results it would be unjustified to attempt to localize the site of ventricular extrasystoles or of bundle-branch block from the direction of the major initial complex in the three leads of the electrocardiogram.

Diamond, Mortimer: Calcification of the Myocardium in a Premature Infant. *Arch. Path.* 14: 137, 1932.

In a twenty-six-week-old, premature infant, who lived with signs of cardiac failure for thirty minutes after birth, extensive calcification of the myocardium was found which is explained as secondary to toxic degeneration of the muscle fibers. The principal findings were in the right auricle which was rigid owing to the presence of yellowish white deposits which to a large extent had singled out the trabeculae carneae, making them appear as distinct, yellowish white linear bundles. The auricle measured 21 by 15 by 12 mm.; its wall was as much as 3 mm. in thickness, and its endocardium was smooth. On microscopic examination, there were extensive deposits of calcium in the right auricle which appeared in the form of coarse and branched trabeculae. In many places the calcification involved the entire thickness of the wall from the epicardium to the endocardium, which was markedly thickened. In the right auricular appendage practically all the muscle fibers had been substituted by calcium, and the derivation of the calcium trabeculae was clearly shown. Not only did the calcium trabeculae imitate the outlines of the muscle fibers, but they also showed their characteristic arrangement. There were some deposits of calcium in the left auricle, although they were less pronounced. Minor changes occurred elsewhere in the heart.

A review of the literature showed that calcification of the myocardium is secondary to preceding degeneration or necrosis of the muscle fibers. This degeneration may be due to vascular, inflammatory or toxic conditions. Fatty degeneration plays no part in calcification of the muscle fibers.

Ernstene, A. Carlton: The Anatomy and Physiology of Congenital Cardiovascular Disease. *New England J. Med.* 207: 523, 1932.

The author divides congenital cardiovascular disease into three major groups: (1) the a-cyanotic group, (2) the group of cases having an arteriovenous shunt with possible transient cyanosis due to reversal of flow through the defect, and (3) the cyanotic group (*morbus caeruleus*), consisting principally of those congenital cardiac defects described as the tetralogy of Fallot, consisting of a defect of the ventricular septum, pulmonary or infundibular stenosis, dextroposition of the aorta and hypertrophy of the right ventricle.

Sprague, Howard B.: Congenital Heart Disease. *New England J. Med.* 207: 525, 1932.

At the present time it is wiser, the author believes, to restrict attempts to the differential diagnosis of the anomalies in the congenital heart disease to the eight

types which are outlined in this paper. It is usually only confusing to think of all the possible combinations of congenital heart defects. If one can be sure of diagnosing the enumerated types, it may lead later to a better differentiation of the more obscure lesions which have not a characteristic combination of clinical signs.

Robey, William H.: *Treatment of Rheumatic Heart Disease.* New England J. Med. 207: 533, 1932.

In this symposium, the more commonly accepted methods of treatment for patients with this form of heart disease are briefly outlined. The control of pain by the use of salicylates and allied drugs, the eradication of foci of infection, particularly the tonsils, and other forms of treatment are mentioned. The author points out that the treatment of rheumatic heart disease during the course of fever is unnecessary and unsatisfactory. He states that one should not hurry into a diagnosis of cardiac lesion or lesions during the height of febrile attacks nor for several weeks after the cessation of fever. The rapidity of heart action plus edema about the valve orifices may distinctly obscure real lesions or simulate lesions in an otherwise normal heart. He states that digitalis is seldom indicated, for it is difficult to estimate its effect upon a heart during the tachycardia of any febrile state.

Breed, William B.: *Diagnosis and Clinical Signs of Rheumatic Heart Disease in Children.* New England J. Med. 207: 530, 1932.

This paper deals principally with the protein forms of the disease as it occurs in children. The author emphasizes the importance of fatigue, irritability, epistaxis, failure to gain weight and muscle pain. Vomiting, chorea, skin manifestations and nodules are also discussed.

Collis, W. R. F.: *The Contagious Factor in the Etiology of Rheumatic Fever.* Am. J. Dis. Child. 44: 485, 1932.

The author has observed an epidemic of nasopharyngeal infection in a group of twenty-five children, convalescing from rheumatism. In all, thirteen children were infected, and in eight of these an acute rheumatic relapse subsequently developed. Following a silent or incubation period of from seven to twenty-four days, various manifestations of rheumatism became manifest. The organism causing this epidemic was the hemolytic streptococcus, but it was only during the height of the throat infection that the organism could be obtained in anything like pure culture from the pharynx. Other epidemics of nasopharyngeal infection were observed in the same ward during this period. One of these was shown to be associated with pneumococcus and another with micrococcus catarrhalis; neither was followed by rheumatic relapses.

A study of these children was made by determining their skin sensitivity to streptococcus exotoxine consisting of a filtrate of a twenty-four-hour broth culture and the endotoxine which was an extract of the ground-up bodies of dried cocci. It was found that the children gave fewer positive reactions with the exotoxine than a similar age group of controls. When tested with the endotoxine, 100 per cent gave positive reactions compared with only 20 per cent of the controls. The author has also studied the incidence of acute streptococcus infections in a group of patients who had not previously had rheumatic fever. It is felt that there is no essential difference in the etiology of primary and secondary attacks of rheumatic fever. In conclusion, the author states that the etiology of rheumatic fever can be explained only when its connection with acute sore throat, caused by the hemolytic streptococcus is understood. It cannot be described as a contagious disease in the ordinary sense of the word, as more than one factor is responsible for its development. A streptococcal infection of the throat is no doubt contagious in the epidemic sense but is followed by rheumatic fever only in certain individuals.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process. 1. Observations on the Ecology of Hemolytic Streptococcus in Relation to the Epidemiology of Rheumatic Fever. J. Exper. Med. 56: 609, 1932.

Certain factors of climate are favorable to streptococcus respiratory diseases. In those tropical environments where hemolytic streptococcus is unusual in the throat flora, scarlet fever is unknown and rheumatic fever rare. In New York City, however, following epidemic waves of pharyngitis with hemolytic streptococcus the incidence of rheumatic fever rises precipitously. The correlation between the geographical distribution of hemolytic streptococcus and rheumatic fever is a definite one.

Furthermore, in New York City during the seasons of the year in which hemolytic streptococcus is seldom recovered from the pharynx, acute attacks of rheumatism are unusual. Corresponding to the seasonal attacks of hemolytic streptococcus infections, the curve of incidence of acute rheumatism shows a similar form.

Among the children of wealthy patients, enjoying great protection, hemolytic streptococcus has been recovered infrequently from the throat, and rheumatism has not been encountered during this study. Among the poor under observation in New York City, however, the organisms is found frequently in the pharyngeal flora and rheumatic fever is common. The findings suggest that poverty and unhygienic living conditions favor both the activity of hemolytic streptococcus in the throat and the incidence of rheumatic fever.

Moreover, localized outbreaks of rheumatism have been observed frequently following epidemics of "sore throat." Bacteriological studies of these upper respiratory infections demonstrate a close relationship between the advent of hemolytic streptococcus in the throat flora and the outbreak of rheumatic fever in susceptible individuals.

In addition to these studies of streptococcus infections and their relationship to the development of rheumatic fever, observations of the rheumatic patient add further emphasis to this association. First, among the group of rheumatic children in an isolated environment, reactivation of the rheumatic process has been recognized only following the advent of hemolytic streptococcus in the throat flora.

Also, an investigation of families in which several members have rheumatic heart disease has led to the same conclusion. Recrudescences of the disease have been observed under a variety of conditions among these individuals. However, the one constant factor in the outbreaks of recrudescences in rheumatic homes is their association with family epidemics of hemolytic streptococcus infection.

Moreover, by studying rheumatic patients before, during and after transplantation to a tropical environment, it has been possible to demonstrate a close relationship between activity of the disease process and infection with hemolytic streptococcus. While the rheumatic patients remained in the tropics, this organism was not recovered from the pharyngeal flora, and the disease process seemed quiescent. On return to New York City, those individuals who have escaped respiratory infection have remained symptom-free. However, of those who have contracted hemolytic streptococcus pharyngitis, each has developed a rheumatic attack within three weeks after infection.

Finally, extensive bacteriological studies made in ambulatory rheumatic subjects over a period of four years have demonstrated that the individuals who escape respiratory disease remain free of rheumatic manifestations. On the other hand, the majority of rheumatic patients who contract hemolytic streptococcus pharyngitis experience shortly afterward a definite recrudescence of their disease. In conclusion, there is a close relationship between respiratory infection with hemolytic streptococcus and activity of the rheumatic process in susceptible individuals.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Relationship of *Streptococcus Hemolyticus* to the Rheumatic Process. II. Observations on the Biological Character of *Streptococcus Hemolyticus* Associated With Rheumatic Disease. J. Exper. Med. 56: 633, 1932.

To determine the nature of the organisms associated with outbreaks of rheumatism at the Pelham Home, in a large number of individuals at the Presbyterian Hospital Nurses' Training School and among rheumatic subjects in New York City under continuous clinical observation, studies of the throat flora have been conducted. Hemolytic streptococcus in most instances appeared in the pharynx from one to five weeks before the onset of the rheumatic attack. These organisms have been investigated with the usual types of bacteriological tests and, in addition, have been classified serologically according to Lancefield's technic. The results have demonstrated that the organisms were not of a single type but fell into six antigenic groups. The majority of the freshly isolated strains tested were strong toxin producers. The organisms producing the strongest toxin were cultures from the patients who developed extremely intense rheumatism. About 70 per cent of these toxins were neutralized by a monovalent streptococcus antiserum.

Coburn, Alvin F., and Pauli, Ruth H.: Studies on the Relationship of *Streptococcus Hemolyticus* to the Rheumatic Process. III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic *Streptococcus*. J. Exper. Med. 56: 651, 1932.

In the first two papers findings were presented which point to a close relationship between the incidence of rheumatic fever and the distribution of *Streptococcus hemolyticus*. The fact was emphasized that in the rheumatic subject a recrudescence of the disease process is usually preceded by pharyngeal infection with hemolytic streptococci. These organisms conspicuous in the throat flora during the period of infection preliminary to an attack of acute rheumatism fell into six antigenic groups and produced toxins which in 70 per cent were neutralized by a monovalent streptococcus antiserum. In the present study, four series of observations have been presented, demonstrating the development of immune bodies to hemolytic streptococcus during the course of rheumatic fever. The agglutination and complement fixation reactions of sera from patients with acute rheumatism suggest recent infection with streptococcus. Precipitin tests indicate that at the time of appearance of the rheumatic attack, individuals develop, in their blood, precipitins to the protein fractions of hemolytic streptococcus. That these precipitins may not be entirely specific is recognized from their cross-reactions with antigens of chemically related organisms. The studies made in association with E. W. Todd of England have demonstrated that at the onset of an attack of acute rheumatism, there occurs in each instance a rise in the antistreptolysin titer of the patient's serum. This titer is much higher than that observed in normal subjects or in patients with bacterial infection other than hemolytic streptococcus. This presence of antistreptolysin with an N.D. of 0.005 c.c. is considered strong evidence of recent infection by hemolytic streptococcus. In conclusion, the relationship between the incidence of hemolytic streptococcus and the geographical distribution of rheumatic fever, the relationship between the recrudescence in the rheumatic subject and infection of the throat with hemolytic streptococcus, the development of immune bodies for hemolytic streptococcus at the onset of the rheumatic attack, and the apparently specific relationship of antistreptolysin formation to infection with hemolytic streptococcus—together this combined evidence indicates that the infectious agent initiating the rheumatic process is *Streptococcus hemolyticus*.

Book Reviews

DIE BLUTDRUCKKRANKHEIT. By Prof. Dr. Otfried Müller and Prof. Dr. Walter Parrisins. Pp. 142, with 72 illustrations. Stuttgart, 1932, Ferdinand Enke.

In this volume Professor Müller, to whom the profession is already indebted for pioneer work in the application of Lombard's method of capillary microscopy in the living to clinical problems, and Professor Parrisins present a study of the hypertensive diseases. The scope of the investigation is indicated by the subtitle: "clinical, hereditobiologic, anthropometric, biochemical, histological, capillary-microscopic, and other investigations on the circulation in hypertensive individuals."

Hypertensive disease is divided into three types:

1. Hypertension associated with inflammatory renal disease.
2. Essential hypertension without organic renal disease.
3. Hypertension associated with the arteriosclerotic contracted kidney.

The fundamental separation of the second and third groups is surprising. The arteriosclerotic kidney is generally regarded as an advanced stage of essential hypertension, and the reviewer is unable to see any evidence in the book that would tend to cast doubt on this well established view.

The three types were investigated from the point of view of their constitutional characteristics. It was found that nephritic hypertension occurs almost always in individuals of asthenic or "leptosomic" habitus, and that evidences of endocrine dysfunction are absent. On the other hand, essential hypertension affects mostly persons of "pyknic" or sthenic habitus, who very often have such endocrine disturbances as obesity, diabetes, or menstrual disorders. In the third group of hypertension with arteriosclerotic kidneys, both main constitutional types were almost equally represented. The hereditary factor is strong not only in essential but also in nephritic hypertension.

To American readers the most interesting part of the book will probably be the investigations on the capillaries. The capillaries of the bulbar conjunctiva, lip, breast, forearm, nail fold, thigh, and other parts were examined during life with the capillary microscope. Many beautiful photographs of the observations are reproduced. In essential hypertension the investigators find that the capillaries present a spastic-atonie picture, i. e., the arterial limb of the capillary is contracted and the venous limb relaxed and full of blood. It is the filling of the venous limb that accounts for the red appearance of these patients. In nephritic hypertension, on the other hand, the capillaries are contracted throughout their course, resulting in pallor. Another interesting observation is that the irritability of the capillaries to mechanical stimulation is increased in essential but not in nephritic hypertension.

The least satisfactory part of the book, to the reviewer, is that dealing with the endocrine disturbances in hypertension. The authors state that they observed changes in the morphology of the capillaries following the administration of thyroid, ovary, testis, or anterior lobe of the pituitary in patients presenting evidences of hypofunction of these glands. The gland preparations were given either by injection or by mouth. They also observed lowering of elevated blood pressure following administration of these endocrine products in appropriate cases. These results, especially with the oral administration of ovarian and testicular preparations, are contrary to general experience in this country, and in view of their great importance should be confirmed before acceptance. Nor does the authors' demonstration of "a tendency to increased tissue acidity" in essential hypertension seem unequivocal.

These researches would not alone, however, have provided the occasion for writing a monograph on "The Cardiac Output of Man in Health and Disease," as Grollman has done, had not the technic of analysis been advanced by his introducing the use of a new agent, acetylene, as an essential factor in his method. The long history of effort in the search for a satisfactory technic is described in detail by Grollman in the first fifty-one pages of his book. Beginning with the early estimates of Senac (1783), Thomas Young (1809), Haller (1757), and the later ones of Volkmann (1850), Edward Hering (1832), Vierordt (1858), Dogiel (1867) and Ludwig's pupils (Meade Smith, Stolnikow, Pawlow, Bohr), he recounts briefly those of Fick (1869-1870) and Hoorweg (1890), Stewart (1897-1921), Zuntz (1892-1898). He then describes the principle introduced by Fick in 1870, and the use which subsequent investigators have made of it. Gréhant and Quinquaud were the first (1886) to apply the principle in dogs. And the first direct estimations of the cardiac output in man were made in 1903 by Loewy and von Schrötter.

The list of those who have employed Fick's principle utilizing either oxygen or carbon dioxide is a long one, and the modifications which each has introduced have been numerous. The relative advantages of each of them as well as the difficulties and the errors inherent in them are analyzed critically and sometimes sharply. Grollman describes also the use of foreign gases, nitrogen, nitrous oxide, ethyl iodide and ethylene and defines both their usefulness and its absence. He criticizes also the various physical methods which have been suggested, the latest being that of Broemser and Ranke (1930) and finally the injection methods. Grollman's own method based on the use of acetylene is described in detail. The development of the method, the choice of this special gas, its fulfillment of the requirements of this particular situation, its solubility and diffusibility, its employment and the calculations which its use permits are all analyzed.

Proof that the acetylene method does in fact measure the cardiac output depends, of course, on the possibility of reproducing previous results, the logical coherence of the procedure and a reference to direct comparison, in this case, with the concentration of acetylene in the mixed venous and arterial bloods. The method seems so far to have satisfied the most rigid tests that have been applied to it. It has limitations; if the cardiac output exceeds 10 liters, the time occupied by a circuit of the blood is too short to permit a sufficient number of breaths to be drawn to mix thoroughly the air in the lungs with the acetylene in the bag. In consequence the blood flowing through the lungs may not enter into equilibrium with the gas. This difficulty Christensen may, meanwhile, have overcome. The other difficulty with the method applies to those clinical situations in which the respiratory apparatus is embarrassed to so great an extent as to interfere with proper mixture of the foreign gas with the air in the lungs.

It was Lindhard (1918) who first showed that the cardiac output bears a relation to the respiratory metabolism. Grollman has now demonstrated the close relationship between the basal metabolism and the cardiac output. Since the basal metabolism is proportional to the surface area, the step which Grollman next took seems logical; he related cardiac output to the surface area. A study of the measurements made so far of normal persons in a basal state shows that the cardiac output per square meter of body surface is 2.2 ± 3 liters per minute and that the average deviation from the mean is only 6.4 per cent.

To be able to make this statement is to announce one of the few important physiological constants observable in the human body. To do so is, as Henderson remarked, to supply exact information on probably "the most important quantitative function of the whole body." Considering the importance of the achievement, it is a pleasure to record the modesty which attends the original descriptions. Grollman has added a method of value, and he has also made a first rate contribution to physiological generalization.

Once in possession of a method apparently reliable, it has been possible to explore situations in which the cardiac output plays a part. In the brief period since 1929, many of them, both in health and in disease, have been studied. Differences in output according to age, especially after forty years, have not yet become known. But the influence of position, of the ingestion of food, of sleep, of sex (and the menstrual cycle), of psychic disturbances, of change in temperature and altitude, and of muscular exercise, have all been investigated, and in each case, with the addition of new light. The insight which knowing the cardiac output yields in learning the action of drugs, especially those which have an influence on the heart and the blood vessels, is, of course, of prime importance. Without knowing the cardiac output, precise knowledge is all but impossible. The action of alcohol, caffeine, and tobacco, or carbon dioxide, of digitalis, of drugs acting on the sympathetic system and of those originating in the organs of internal secretion have all been studied, in some cases so far, however, only in a preliminary way.

There are chapters also, dealing with the cardiac output in disease, in congenital heart disease, in the various heart and circulatory diseases of adult life and finally with its correlation with other physiological functions of the organism, such as metabolism, pulse rate, the velocity of the blood flow, the blood pressure and the size of the heart.

To describe the results of the investigations of these various matters would carry this description beyond the requirements of a review. They are in any case given with brevity and with clearness in the chapters themselves of this book.

Where there is so much to praise, the duty of calling attention to small blemishes is the more onerous. There are a few incorrect references in the early pages (Stewart on page 7, should read 433 instead of 423, Bauman and Lanter on page 11, should read 29 instead of 27, Loewy and von Schrötter on page 13 should read 320 instead of 32). The use of the word "determination," in accordance with a custom become all too common, is employed where "measurement" or "estimate" was formerly used. Where inquiry is being made, is there not something incongruous in using a word in which the operation of the will is, at least, intimated? "On" instead of "in" is also becoming usual in speaking of experiments or measurements in connection with animals or men, without corresponding increase in the beauty of the language. With the word data, a plural form, appears the adjective "this." "Boemser" is spelled without an r (page 175) and "die" is spelled with one (page 294, ref. 157). But on the credit side there are two pages (3 and 4) of terms accurately defined which should, because of their sensibleness, aid in dislodging many others which have encumbered the literature of this subject to its own confusion.

These are after all small matters. Of greater importance is the welcome which it is pleasure to accord a distinguished research.

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THE MECHANISM OF PRODUCTION OF SHORT P-R INTERVALS AND PROLONGED QRS COMPLEXES IN PATIENTS WITH PRESUMABLY UNDAMAGED HEARTS: HYPOTHESIS OF AN ACCESSORY PATHWAY OF AURICULO-VENTRICULAR CONDUCTION (BUNDLE OF KENT)*

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IN 1930, Wolff, Parkinson and White¹ called attention to a group of cases with the following characteristics: (a) The patients are usually young healthy individuals without evidence of organic heart disease. (b) Their electrocardiograms show short P-R intervals (0.10 second or less), and ventricular complexes with certain characteristics suggesting bundle-branch block. (The QRS complex is widened and slurred, and the T-wave may be opposite in direction from the main deflection of QRS.) (c) In some cases both the P-R interval and the ventricular complex suddenly revert to normal, without change in contour of the P-wave. This may occur spontaneously or when the heart rate is increased by exercise or by atropine administration. When the heart rate slows the abnormal characteristics may return. Vagal stimulation effected a return of aberrant complexes in one case.¹ (d) The patients in this group are particularly liable to attacks of paroxysmal supra-ventricular tachycardia or paroxysmal auricular fibrillation, during which the ventricular complex assumes a normal configuration.

Prior to the publication of Wolff, Parkinson and White, somewhat similar cases had been reported by Wilson,² Wedd³ and Hamburger.⁴ Since that time, Pezzi⁵ has reported three of them.

We have had the opportunity of studying nine cases of this type. One other case in our series was furnished by the kindness of Dr. W. B. Porter of Richmond, Va. The significant data concerning them are summarized in the appended case reports. Only two patients in our group had demonstrable organic cardiovascular disease (Cases 7 and 9). Four

*From the Robinette Foundation, Medical Division, Hospital of the University of Pennsylvania.

gave a history of paroxysmal tachycardia. One patient, fourteen years of age, had had such attacks since the age of two years (Case 1). Two individuals had paroxysmal auricular fibrillation (Cases 2 and 10). A reversion of the electrocardiogram to normal could not be produced in any of our cases, either by exercise or by atropine administration. In one patient (Case 1, Fig. 1), the ventricular complex assumed a normal contour during a paroxysm of tachycardia. Graphic records were not obtained during a paroxysm in any other case. In one of the patients with cardiovascular disease (Case 7) electrocardiograms were ob-

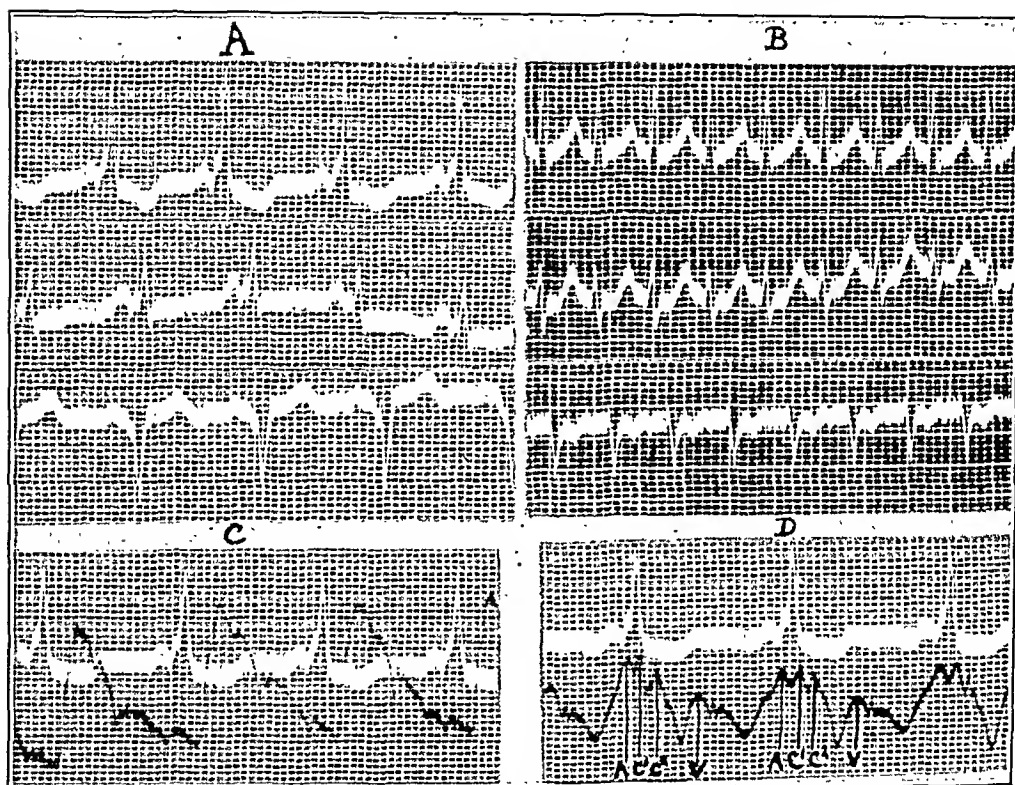


Fig. 1.—Case 1. A, Electrocardiographic tracing made on March 22, 1932. The P-R interval has a duration of 0.09 second. The QRS complex is widened and slurred, duration 0.11 second.

B, Electrocardiogram taken April 5, 1932, during a paroxysm of tachycardia. The widening and slurring of the QRS complexes has disappeared. The heart rate is 215 per minute. The electrical axis has not changed.

C, Simultaneous electrocardiogram and carotid pulse curve recorded without parallax. The carotid tracing was made with an optical recording device.¹⁰ The upstroke of the carotid pulse curve takes place 0.08 to 0.09 second after the peak of the R-wave of the electrocardiogram.

D, Simultaneous electrocardiogram and jugular phlebogram recorded without parallax. The phlebogram was made with an optical recording apparatus.¹⁰ The A- and V-waves are readily identified. The C-wave is bifurcated. The upstroke of the second component (C₂) begins 0.08 second after the peak of the R-wave of the electrocardiogram. It therefore occurs at the same time in the cardiac cycle as the carotid upstroke (see Fig. 1 C). The upstroke of the first component of the C-wave (C₁), precedes the upstroke of the second component (C₂) by 0.08 to 0.09 second. It precedes the peak of the R-wave of the electrocardiogram by about 0.01 second.

tained on two occasions, eight days apart (Fig. 2). The first tracing was characteristic of the group under consideration; the heart rate was 120. The second showed a different type of complex; the rate was 105. The presence of severe progressive heart disease makes it impossible to

draw any conclusions concerning the effect of rate change upon the occurrence of the characteristic short P-R interval and aberrant ventricular complex in this patient. In the other patient with heart disease (Case 9, Fig. 3) the electrocardiogram in 1927 showed a short P-R interval and wide QRS complex. In 1932 these characteristics had disappeared and could not be made to reappear by vagal stimulation.

Our interest in this group of cases is chiefly centered in an attempt to understand the nature of the abnormal cardiac mechanism by which this unusual electrocardiographic picture is produced. Before under-

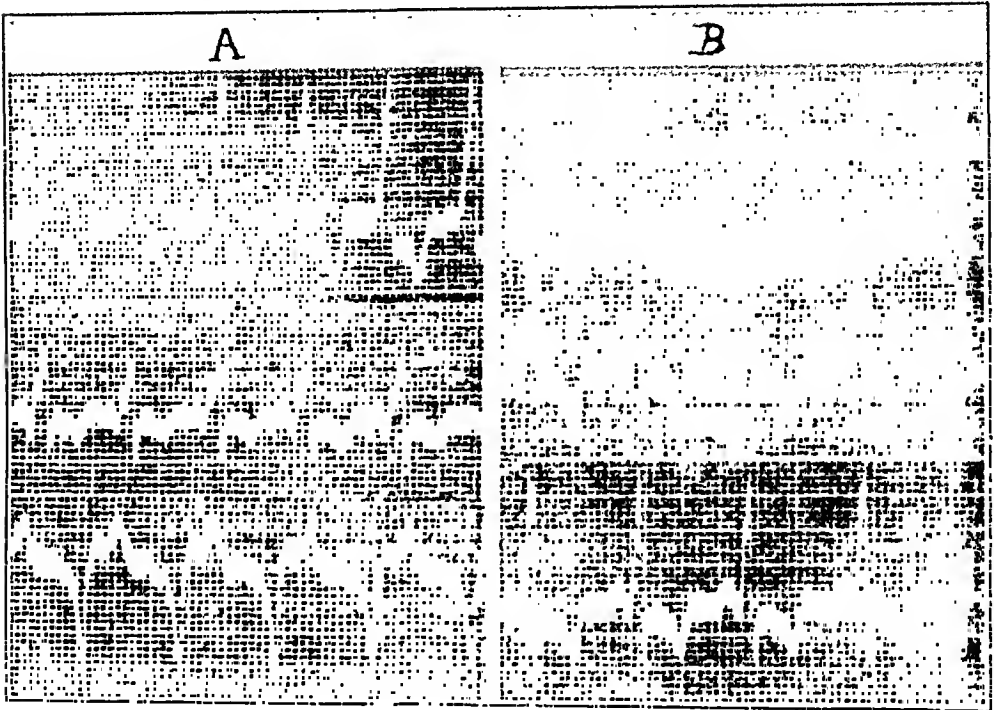


Fig. 2.—Electrocardiograms of Case 7. A, Tracing made November 13, 1925. P-R interval 0.08 second. QRS complex widened and slurred in its initial deflection, duration 0.12 second.

B, Tracing made November 21, 1925. P-R interval is still short. The QRS complex is still widened but has changed its contour considerably. The T-waves have also changed markedly. There is probably some overshooting in Leads II and III. This patient had severe progressive cardiovascular disease.

taking a discussion of this question, we wish to emphasize three additional features presented by these patients: (a) The period elapsing from the beginning of the P-wave to the end of the QRS complex is well within normal limits, despite the aberration of the ventricular complex. (b) If the P-R interval lengthens, the QRS complex simultaneously shortens to an equal extent. Consequently in a given case, the period from the beginning of the P to the end of QRS remains substantially the same throughout, whether the electrocardiogram is normal or abnormal. (Cf. Wolff, Parkinson and White,¹ Cases 3 and 4.) (c) In the cases so far reported, the slurring of the QRS complex has always involved the initial deflection. The terminal portion may or may not be slurred.

Two hypotheses have been proposed to explain the abnormal cardiac mechanism:

I. Wolff, Parkinson and White¹ have described it as a bundle-branch block. Such a view was probably suggested by the fact that widened and aberrant QRS complexes have always been associated with the conception of defective intraventricular conduction. However, this explanation is untenable for the following reasons: (1) The time interval from the beginning of P to the end of QRS does not exceed that of normal cases. Furthermore, when the mechanism reverts to normal, this interval shows no material change—since the lengthening of the P-R interval and the

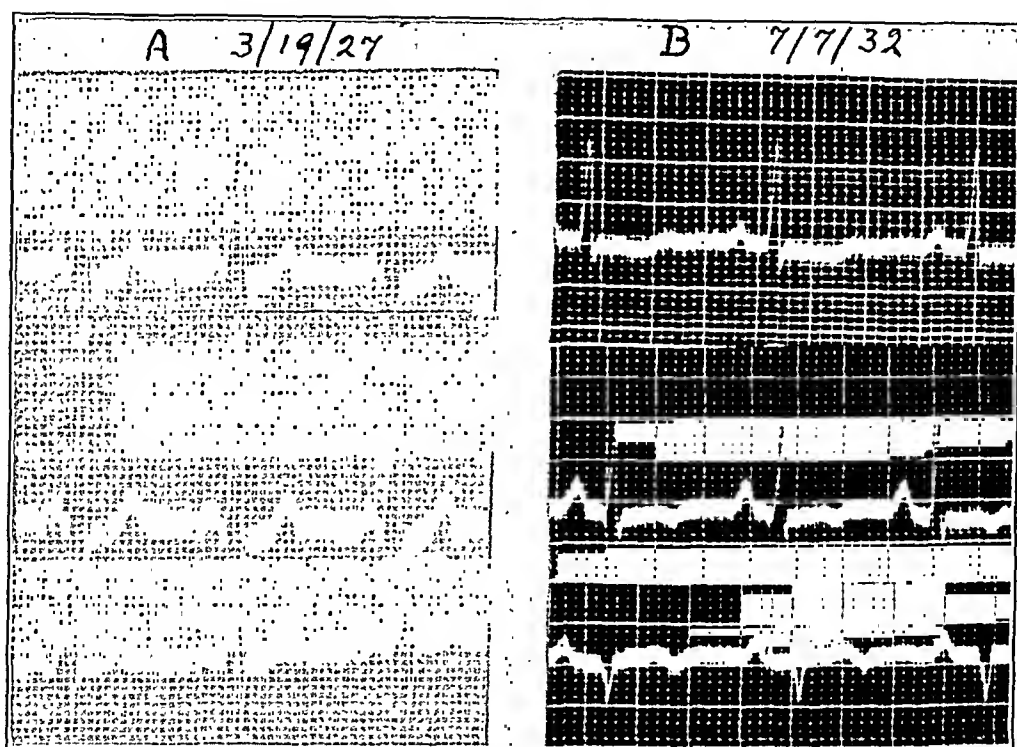


Fig. 3.—Electrocardiograms of Case 9. A, Tracing made March 19, 1927. The P-R interval is 0.10 second. The QRS complex is widened and slurred in its initial deflection, duration 0.12 second.

B, Tracing made July 7, 1932. The P-R interval is now normal, 0.18 second. The QRS complex is of normal width, 0.06 second. The abnormal characteristics did not return on vagal stimulation. This patient has definite rheumatic heart disease.

shortening of the QRS complex are approximately equal. (2) The effect upon the electrocardiogram of change in cardiac rate in these cases differs fundamentally from the effect of rate change upon true bundle-branch block. Herrmann⁶ has reported cases of paroxysmal bundle-branch block, in which the conduction defect did not appear until a critical rate was exceeded. We have had a similar experience in a few cases. Moreover, it is well known that defects in intraventricular conduction are often observed in the most premature beats of auricular fibrillation, and in auricular extrasystoles which closely follow the preceding cardiac condition. Therefore, in the presence of an incipient

bundle-branch defect, an increase in heart rate should tend to cause the defect in conduction to appear, not to disappear.* If the cases under consideration really were instances of bundle-branch block, the aberration of the QRS complex should be present during paroxysms of rapid heart action, not absent. (3) The bundle-branch block hypothesis fails to explain: (a) the predisposition of these patients to attacks of paroxysmal tachycardia and fibrillation; (b) the fact that this condition is apparently unrelated to cardiac damage; and above all (c) the short P-R interval. An analysis of the tracings of these individuals shows that *the abnormality of the QRS complex consists, not of a block or delay, but of an actual early arrival in the ventricular muscle of the impulse from the auricle.*

II. Pezzi⁵ objects to the bundle-branch block hypothesis because it does not account for the short P-R interval. He proposes another explanation, namely, that the abnormal mechanism consists of a "paraseptal rhythm." By this term he means a rhythm whose pacemaker is situated in the neighborhood of Tawara's node, in the auricular septum. The etiology of this abnormal rhythm is considered to be an irritative lesion involving the "paraseptal" region. Pezzi accounts for the various phenomena as follows: (1) The short P-R interval is due to the proximity of the pacemaker to the junctional tissues. (2) The P-wave is upright and not inverted (as one would expect, with a paraseptal pacemaker), because the impulse reaches the auricular muscle from the normal direction. The author is not absolutely clear in his exposition of how this is brought about. He implies, however, that the impulse travels direct from the paraseptal pacemaker to the sino-auricular node over a special "sinonodal pathway" before reaching the auricular muscle. It then invades the auricle from the region of the sino-auricular node. This explanation helps further to account for the shortness of the P-R interval, since a period elapses between the discharge of the impulse from the paraseptal pacemaker and its arrival in the auricular muscle via the sinonodal pathway and the sino-auricular node. (3) The aberrant QRS complex is explained as follows: The author assumes the existence of special septoventricular conduction pathways: that, beginning in the node of Tawara, there is a complete functional separation of the junctional tissues into those sending impulses to the right ventricle, and those transmitting them to the left. He believes, therefore,

*This statement must be qualified as follows: Vagal stimulation is known to cause (a) Slowing of the heart rate, which per se aids junctional conduction, and (b) impairment of auriculoventricular conduction. If, therefore, a retardation of rate is vagal in origin, it might be accompanied by impaired conduction of the excitatory impulse through the junctional tissues; since it is theoretically possible for (b) to overshadow (a). Danielopolu¹¹ has actually observed this phenomenon in a bundle branch. However, if the widened QRS complexes in these cases are to be explained by vagal inhibition of conduction, how can one account for the shortened P-R interval? The vagus can hardly be expected to have a "paradoxical effect": both to accelerate and to retard conduction at the same time. Moreover, in one of our patients the vagus was pressed upon in the neck during an attack of paroxysmal tachycardia (Case 1). Thus, presumably, both factors (a) and (b) were operating simultaneously to impair conduction. Nevertheless, the QRS complexes, which were normal during the paroxysm, remained so despite the vagal stimulation.

that the impulses to one ventricle can be blocked by a lesion situated at any point in one of the "septoventricular conduction pathways": (a) In the bundle branch; (b) in the bundle of His, or (c) in the node of Tawara itself. With the foregoing speculation as a point of departure, Pezzi states that the lesion responsible for this group of cases is situated in the neighborhood of Tawara's node but extends to involve part of the node and its "annexes." Thus it blocks one septoventricular pathway at its head, in the node of Tawara, and produces an electrocardiographic picture similar to that of a bundle-branch block. (4) The "irritative lesion in the paraseptal region" is considered to be responsible for the frequently observed paroxysms of tachycardia. (5) None of Pezzi's cases showed a transition from abnormal complexes to normal ones. He explains the occurrence of this phenomenon in the cases reported by Wolff, Parkinson and White¹ by supposing the lesion in those instances to be a very mild one (almost entirely "functional"). A release of vagal tone caused it to disappear, thereby allowing normal conduction through the node of Tawara. Although he does not say so, he must believe that when the transition occurs, the sino-auricular node assumes its normal function of pacemaker.

If all the physiological substructure upon which Pezzi's hypothesis is based were sound, the unusual electrocardiographic picture might be accounted for on this basis. However, the following facts make one question the validity of his explanation: (1) Although the existence of a special sinonodal pathway has been advocated by some authors,* it seems strange that (a) it is not brought into play in other cases of nodal rhythm: (in the vast majority of cases of nodal rhythm, the P-wave is inverted in Leads I and II), and (b) that it comes into play in every single case in this group: (not one case in all those reported shows an inverted P-wave in Leads I or II). (2) There is no evidence of the existence of "special septoventricular conduction pathways" to each ventricle, which are functionally separated from each other as high as the node of Tawara. Lewis^{7a} states, "It is a matter of indifference whether the impulse originates in the normal pacemaker, in the substance of either auricle, or in the A-V node or bundle down to the point of its subdivision; the ventricle is activated in precisely the same way and the resultant curve is of constant form." If functionally isolated "special septoventricular conduction pathways" existed, one would expect aberration of the ventricular complex to be the rule with the pacemaker situated in the node, or in the bundle of His: the pacemaker would have to be located in one of these pathways and should be incapable of transmitting impulses to the other. (3) It is inconceivable that a dislocation of the pacemaker from the paraseptal region to the sino-auricular node could take place without any change: (a) in the rate or rhythm, (b) in the interval from the beginning of the P-wave to the

*It is not accepted by Lewis.^{7a}

end of the QRS complex, or (c) in the contour and direction of the P-wave. (Cf. Wolff, Parkinson and White,¹ Cases 3 and 4.) In our experience, whenever the pacemaker has moved from the region of the node of Tawara to the sino-auricular node, the P-wave has always shown a change in contour and direction. (4) The second objection to the bundle-branch block hypothesis seems applicable to Pezzi's explanation. (5) Pezzi's hypothesis might account for paroxysms of nodal tachycardia. However, it still leaves unexplained the origin of paroxysms of auricular fibrillation, which occurred in one case reported by Wolff, Parkinson and White¹ and in two of our patients. (6) Pezzi speaks of the etiological factor as a "lesion." However, all indications point to an absence of any acquired cardiac damage.⁶

In view of the foregoing considerations, the two hypotheses which have been proposed seem inadequate to explain all the features presented by this group of cases. If, however, the assumption is made that an accessory pathway for auriculoventricular conduction exists, besides that furnished by the bundle of His, the phenomena thus far observed may be accounted for.

Many years ago, Kent⁸ described a structure bridging the auriculoventricular groove at the right lateral border of the heart, connecting the right auricle and right ventricle. It was first observed in newborn rats, but later also in man. Photomicrographs of its appearance in the human heart are available. A statement concerning the frequency of its occurrence in man has not been found. At the upper end of this connection is a node, comprised of tissue similar to that found in the node of Tawara. The muscular bridge begins at the lower border of this node. It is formed by muscle fibers derived from two or three different layers of the ventricular wall. Kent demonstrated to his own satisfaction that impulses could be conducted from auricle to ventricle by this structure in several species of mammals. His conclusions seem justified, namely, that there is a muscular connection between the auricles and ventricles at the right lateral border of the mammalian heart; that this connection has been shown to conduct impulses from auricle to ventricle in mammals and should be capable of doing so in man.

Lewis^{7b} states that "There is no reason to believe that the structures described by Kent take part in conducting impulses from auricle to ventricle. The physiological evidence is strongly opposed to this idea, and such anatomical evidence as we possess is insufficient to give the view any material support." Consequently interest in the "bundle of Kent" appears to have waned. It seems to us, however, that the assumption of conduction of the excitatory process by Kent's bundle,[†] in addition to its conduction by the conventional pathway through the bundle

⁶Wolff, Parkinson and White¹ observed that a compensatory pause regularly followed a ventricular extrasystole in these cases. They cited this as evidence in ruling out nodal rhythm. We agree with Pezzi that this fact does not rule out nodal rhythm.

[†]Or some analogous structure.

of His, offers a satisfactory explanation for these cases. It is necessary to assume in addition that this structure is sufficiently developed to function in only a few individuals.

On the basis of a functioning bundle of Kent, the various phenomena observed in these cases may be accounted for as follows:

(1) The shortness of the P-R interval is due to the short direct pathway from auricle to ventricle through Kent's bundle.

(2) The premature invasion of a certain section of the ventricular muscle by this impulse causes (a) a slurring of the initial deflection of the QRS and (b) a widening of the QRS complex at the expense of the P-R interval. (See Fig. 4.)

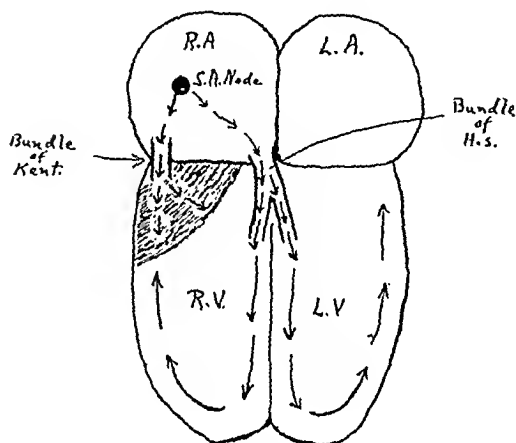


Fig. 4

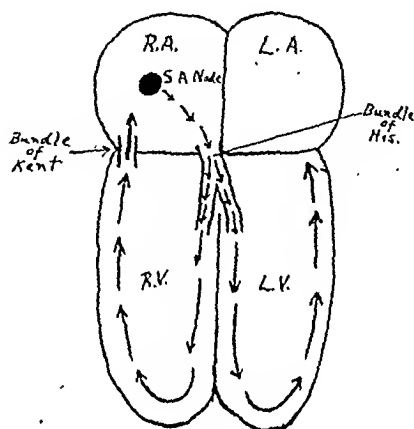


Fig. 5

Fig. 4.—Schematic representation to illustrate the hypothesis of premature transmission of the impulse through the bundle of Kent to the right ventricle. The shaded area represents the section which is activated before the impulse reaches the ventricles through the bundle of His. This mechanism would account for the short P-R interval, the widening of the QRS complex and the slurring of its initial deflection.

Fig. 5.—Schematic representation showing the path of an impulse which might be responsible for exciting a paroxysm of supraventricular tachycardia or auricular fibrillation.

(3) In some cases, conductivity in the bundle of Kent may not be highly developed. Consequently, when subjected to the passage of impulses at a rapid rate, as during paroxysmal tachycardia, it may fail to function. This seems to offer a more satisfactory explanation for the transition from abnormal to normal complexes than that furnished by either of the previous hypotheses (q.v.).

(4) The frequency of paroxysmal tachycardia and paroxysmal fibrillation may be accounted for on the basis of this hypothesis. Kent showed that retrograde conduction through the "right lateral bundle" was possible in newborn rats.⁸⁴ Under certain circumstances, therefore, a retrograde impulse might travel from ventricle to auricle at a time when the physiological state of the auricular muscle would favor the inception of an abnormal rhythm. (See Fig. 5.)

(5) The assumption of a functioning bundle of Kent does away with

the necessity of postulating a lesion, or a defect in conduction, in youthful patients, without evident cardiac damage.*

(6) As we have stated above, when the mechanism changes from a short P-R interval and a wide QRS complex to a normal P-R interval and a normal QRS complex, the duration of the interval from the beginning of the P-wave to the end of the QRS complex tends to remain constant. (Cf. Wolff, Parkinson and White,¹ Cases 3 and 4.) If these facts are confirmed by more extended observation, only one interpretation seems possible, namely: that the variable factor is early aberrant conduction from auricles to ventricles. This does not interfere with conduction through the junctional tissues (the node of Tawara and bun-

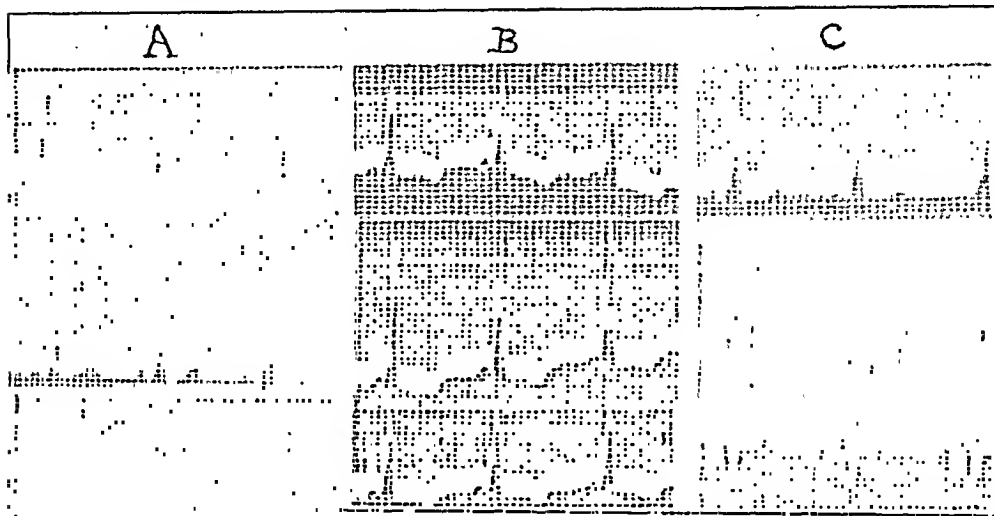


Fig. 6.—A, Electrocardiogram of Case 4, taken December, 1929. The P-R interval is 0.08 second. The QRS complex is widened and its initial portion is slurred, its duration being 0.10 second. There is a Q-wave in Lead III.

B, Electrocardiogram of Case 6, taken September 21, 1931. The P-R interval is 0.08 second. The initial portion of the QRS complex is slurred. The complex has a duration of 0.08 second.

C, Electrocardiogram of Case 5 taken January 7, 1929. The P-R interval is 0.09 second. The QRS complex is widened and slurred, duration 0.11 second.

dle of His), but alters the duration and form of the initial portion of the ventricular complex in direct correspondence with the prematurity of arrival of the aberrant impulse in the ventricular muscle.

(7) If early transmission of the impulse by way of Kent's bundle is the mechanism responsible for this syndrome, (A) there should be definite asynchronism in the contraction of the two ventricles, and (B) the left ventricle should contract at the normal time in the cardiac cycle, whereas the right ventricle should contract prematurely. The data thus far obtained in this group of patients suggest that these things actually occur.

*It is of interest to note that this type of electrocardiogram seems to be quite unusual after the age of forty years. This raises the question as to whether these patients die young (which seems unlikely, since they usually have no evidence of cardiovascular damage); or whether the mechanism responsible for the short P-R interval and the aberrant QRS complex becomes less capable of functioning with advancing years (cf., Case 9, and Wolff, Parkinson and White,¹ Cases 3 and 8).

(A) The evidence for asynchronous contraction of the ventricles is as follows: (a) The electrocardiographic tracings suggest it; (b) a marked reduplication of the first heart sound has been noted in our last two cases. Although no special attention had been paid to this feature in the other six, the records of two state that the first heart sound "was split"; (c) in the one patient in whom a jugular phlebogram was made, there is a bifurcation of the C-wave with an interval of 0.09 second between its two components (Fig. 1 D).^{*} It is well known that optically recorded jugular pulse curves in presumably normal individuals may show a bifurcation of the C-wave. The two elements of this bifid wave are, first, a "venous" wave produced by right ventricular contraction and transmitted up the superior vena cava to the jugular vein; and, second, an arterial wave, which is a transmitted pulsation from the carotid artery. In normal individuals, the interval between the upstrokes of the two peaks of the C-wave does not exceed 0.048 second.^{9, 10} Therefore, the interval (0.08 to 0.09 second) obtained in the patient under consideration is nearly twice the top normal figures. It is comparable to that seen in cases of true bundle-branch block.¹⁰

(B) The evidence that the left ventricle contracts at the normal time in the cardiac cycle, whereas the right ventricle contracts prematurely, is as follows: An optically recorded jugular phlebogram and simultaneous electrocardiogram were photographed on the same film without parallax (Fig. 1 D). A simultaneous carotid pulse curve and electrocardiogram were obtained in a similar manner (Fig. 1 C). A comparison of the carotid and jugular curves with the electrocardiographic tracing shows that: (a) The upstroke of the carotid wave and the upstroke of the second element of the jugular C-wave, C², occur simultaneously in the cardiac cycle at a point 0.08 second after the peak of the R-wave. There is little doubt that both these waves are produced by left ventricular activity. Moreover, the interval separating their upstrokes from the peak of the R-wave is normal.^{9, 10} Therefore, one is probably justified in assuming that left ventricular contraction occurs at a normal time in the cardiac cycle and causes the second peak of the C-wave in the jugular phlebogram. (b) The upstroke of the first element of the jugular C-wave, C¹, precedes the aforementioned left ventricular phenomena by 0.08 to 0.09 second, and precedes the peak of the R-wave by 0.01 second. There is no doubt, therefore, that this wave clearly precedes left ventricular contraction. Since C¹ is almost certainly related to right ventricular activity, the conclusion is difficult to escape that the right ventricle contracts prematurely in the cardiac cycle and at a considerable interval before the left. A great deal of emphasis cannot be

^{*}A jugular phlebogram published by Wolff, Parkinson and White¹ in a similar case does not show a bifurcated C-wave. However, in order to record this phenomenon, an optical recording apparatus must be used, and special attention must be paid to the pressure at which the recording capsule is applied to the jugular vein. By increasing the pressure, the venous element of the C-wave can be diminished or abolished, and the arterial element can be exaggerated.

placed upon the data from a single case. Further observations of this type are necessary. Should it be found that these phenomena occur with regularity, the hypothesis we have presented should be considerably strengthened.

The direction of the initial deflection of the QRS complex deserves mention. If premature activation of a certain constant section of the right ventricle through the bundle of Kent is the cause of the slurring of the initial deflection of the QRS complex, one might expect to find this initial deflection to be in the same direction in every patient. Analysis of the cases so far reported shows that this expectation is not fulfilled. In Lead I, the initial deflection in every case has been upright. In Lead II, 22 have been upright, 4 have been down. In Lead III, 12 have been upright, 14 have been down.* However, this does not constitute a major objection to the hypothesis herein proposed. Variation of position and shape of the heart, or a variation in the location of the bundle of Kent† might readily account for these differences.

The case reported by Hamburger¹ merits a brief discussion, because it presents certain phenomena which have not been observed in any other instance of this syndrome. The presence of an acute febrile illness and a paroxysm of ventricular tachycardia suggests that complicating factors are present in this case, which makes it differ in certain respects from other similar ones. The features of particular interest to us are the following: (1) This is the only case on record in which the abnormal complexes have persisted during a paroxysm of supraventricular tachycardia, if we admit the correctness of this electrocardiographic diagnosis. (It is possible, however, that the rhythm is a simple tachycardia.) (2) During the "paroxysmal tachycardia" the rhythm is frequently interrupted by beats with a normal P-R interval and a normal ventricular complex. An examination of Hamburger's tracings shows that: (a) The interval from the beginning of the P-wave to the end of the QRS complex remains quite constant, whether the ventricular complex is normal or abnormal. This suggests that the beat with the normal ventricular complex is a sequential beat, not a nodal beat (cf. Hamburger's explanation). (b) There is an inverted P-wave after each normal QRS complex, more apparent in Leads II and III. (c) The interval between the beginning of such an aberrant P-wave and the next normal P-wave slightly exceeds the length of the usual auricular cycle. This disturbance in the rhythm is therefore like that seen when any auricular rhythm is interrupted by a beat from a different auricular focus.

The only satisfactory explanation of these phenomena which occurs to us, is that afforded by the "bundle of Kent hypothesis." It might

*Case 9 of Wolff, Parkinson and White¹ is not included in this analysis, since Lead III is not available.

†Kent does not deny the existence of other analogous auriculoventricular connections.

be outlined as follows: In Hamburger's patient, the bundle of Kent has a highly developed conductivity, being capable of conducting impulses at a rate of 150 per minute. However, at this rapid rate it occasionally fails to function. At such a time the impulse from auricle to ventricle is conducted solely through the bundle of His, hence the P-R interval and QRS complex suddenly become normal, although the interval from the beginning of the P-wave to the end of the QRS complex remains substantially unchanged. Now, by the time the impulse has extended throughout the ventricle, the bundle of Kent, having had a rest period, is once more conductive. It therefore conducts the impulse in a retrograde direction back to the auricle and gives rise to an inverted P-wave directly following the normal QRS complex.* This auricular beat has the same effect upon the pacemaker that an ordinary auricular extrasystole would have. It abolishes the impulse which is forming and gives rise to a pause, since an entirely new impulse must be built. After this the "paroxysmal tachycardia" begins once more. The demonstration of probable retrograde conduction through the bundle of Kent in Hamburger's case affords support to the explanation we have suggested to account for the frequency of paroxysmal tachycardia in these cases (q.v.).

SUMMARY

(1) In about one out of a thousand electrocardiograms, a case may be encountered which exhibits an abnormally short P-R interval associated with a widened QRS complex, markedly aberrant in its initial portion.

(2) It is necessary, as stressed by Wolff, Parkinson and White,¹ to recognize that this type of tracing may occur in the absence of acquired cardiac damage.

(3) Many of these patients are subject to paroxysms of tachycardia and auricular fibrillation.

(4) An analysis of the tracings of these cases reveals that their characteristics cannot be explained, by the hypothesis that they are due either to bundle-branch block (Wolff, Parkinson and White¹), or to "paraseptal rhythm" (Pezzi⁶).

(5) The abnormal mechanism consists, not of a delay or block, but of an actual acceleration of the passage of the impulse from the auricle to a section of the ventricle.

(6) All the data so far obtained are in keeping with the possibility that an accessory pathway of A-V conduction (such as that described by Kent,⁸ between right auricle and right ventricle) could be responsible for the phenomena manifested by these cases.

(7) We therefore propose this new hypothesis. We recognize clearly

*It is not improbable that certain cases of so-called reciprocal rhythm are explainable by retrograde conduction through the bundle of Kent.

that it is only an *hypothesis*. Nevertheless it seems a strikingly satisfactory one and accounts for all the phenomena thus far observed in this syndrome.

CASE REPORTS

CASE 1.—V. D., a white female, aged fourteen years, had suffered from paroxysms of tachycardia about once a week since the age of two years. She was first seen on March 22, 1932. Examination showed no evidence of cardiovascular disease. Both heart sounds were reduplicated. The orthodiagram was normal.

The electrocardiographic studies are shown in Fig. 1. Vagal pressure did not cause any change in the tracing. Exercise increased the heart rate to 125 beats per minute, without changing the electrocardiogram. On April 5, 1932, the patient was studied during a paroxysm of tachycardia. Fig. 1 B shows the tracing. Vagal pressure did not stop the paroxysm nor change the electrocardiogram. Further studies are shown in Fig. 1 C and D.

CASE 2.—R. B., a white male, aged thirty-four years, had experienced occasional paroxysms of rapid heart action since the age of eighteen years. In February, 1932, while playing golf, he suddenly became conscious of rapid irregular heart action. Dr. Richard Anderson of Burlington, N. J., examined him and found that he had "an auricular fibrillation with a pulse deficit of about 60." This paroxysm continued for four days. Dr. Anderson referred the patient to one of us on March 10, 1932. There was no evidence of cardiovascular disease. Both heart sounds were markedly reduplicated. The orthodiagram was normal.

An electrocardiogram was made on March 10, 1932. It is not reproduced since it markedly resembles the tracing of Case 1 (Fig. 1). The P-R interval is 0.08 second. The QRS complex is widened and its initial deflection is slurred—duration 0.12 second. The T-waves are opposite in direction to the initial deflection of QRS. Exercise increased the heart rate to 125 beats per minute, without altering the electrocardiogram.

CASE 3.—A. B., was a white male, aged nineteen years, a student at the University of Pennsylvania. He had his electrocardiogram taken on December 13, 1929, when a routine study of a series of normal students was being made. He had no complaints and no signs of cardiovascular disease. The orthodiagram was normal. The first heart sound was markedly reduplicated. The electrocardiogram is not reproduced since it resembles that of Case 1 (Fig. 1). The P-R interval is 0.08 second. The QRS complex is widened and its initial deflection is slurred, duration 0.12 second. Exercise increased the heart rate to 145 beats per minute and amyl nitrite administration raised it to 155, without changing the electrocardiogram. A re-examination was made February 13, 1931. No change had taken place in the interval.

CASE 4.—W. H. L., Jr., a white boy of thirteen years, was found to have an abnormal electrocardiogram during a routine medical examination. He had no complaints and no signs of cardiovascular disease. The orthodiagram was normal. An electrocardiogram was made in December, 1929 (Fig. 6 A). Exercise increased the heart rate to 130, without changing the electrocardiogram. There has been no change in the state of his health since the first examination.

CASE 5.—T. B. G., a college boy of twenty-one years, had rowed on the crew for three years. He had no signs or symptoms of cardiovascular disease. His electrocardiogram (Fig. 6 C) was taken January 7, 1929, during a routine study of the hearts of a group of college athletes. No follow-up examination has been made.

CASE 6.—H. B., a white woman of thirty-five years, had suffered from fatigue and undernutrition for several years. She had experienced "choking spells" for

two years, lasting from a few minutes to several hours. Her heart rate had never been taken during one of these spells. She was first seen September 21, 1931. She had no evidence of cardiovascular disease. The orthodiagram was normal. Her electrocardiogram is shown in Fig. 6 B. The heart rate was increased to 125 by exercise, and to 155 by amyl nitrite, without changing the electrocardiogram. She was last heard from on July 5, 1932; at that time she was suffering from "nervous exhaustion."

CASE 7.—H. L., a white male of twenty-seven years, was a patient in the University of Pennsylvania Hospital from November 12 to 30, 1925. He had evidence of severe congestive heart failure and chronic glomerulonephritis. The heart was markedly enlarged. At one time a pericardial friction rub was heard. The notes state that the first heart sound was "markedly split." He had suffered with "spells of palpitation" for four weeks. Short paroxysms of tachycardia were noted while he was in the hospital. Two electrocardiograms were taken (Fig. 2 A and B). The patient grew progressively worse and signed his release on November 30, 1925. He probably died shortly thereafter.

CASE 8.—(We are able to report this case through the kindness of Dr. W. B. Porter of Richmond, Virginia, who sent us the records.) D. A., was a white boy of fourteen years. During a routine examination on March 21, 1931, he was found to have an abnormal electrocardiogram. He had no complaints and no evidences of cardiovascular disease. The electrocardiogram is not reproduced because it is very much like that of Case 6 (Fig. 6 B). The P-R interval is 0.06 second. The QRS complex is widened and its initial deflection is slurred, duration 0.12 second.

CASE 9.—L. K., a white male is now twenty-eight years old. He was first seen on March 28, 1927, when he was a patient in the Hospital of the University of Pennsylvania with acute rheumatic fever. His rheumatic history dated back to 1917, when he had his first acute attack. In 1927 he had evidence of moderate cardiac enlargement; the blood pressure was 140/40 mm. There were signs of aortic insufficiency and mitral insufficiency and stenosis, but no evidence of congestive failure. He was discharged May 28, 1927. He was seen again on July 7, 1932. His rheumatic infection had apparently been quiescent for at least four years. The cardiovascular findings were similar to those found in 1927. His functional classification is now Class II-A. Electrocardiographic studies were made March 19, 1927, and again July 7, 1932. The former (Fig. 3 A) showed a short P-R interval and wide QRS complex. The latter (Fig. 3 B) showed no abnormality of the P-R interval or QRS complex. Vagal stimulation, by pressure in the neck and ocular pressure, did not cause any change in the electrocardiogram. The interval from the beginning of the P-wave to the end of the QRS complex is 0.22 to 0.24 second in both tracings.

CASE 10.—(We are able to report this case through the kindness of Dr. David A. Cooper.) S. G. was a white male, aged sixty years. He was first seen in 1927 on account of attacks of palpitation and dizziness. He was seen by a physician in one of these attacks on November 11, 1930, and was found to be fibrillating. A diagnosis of myocardial disease was based upon the occurrence of paroxysmal auricular fibrillation. He was first seen by us on January 29, 1930. An electrocardiogram showed a P-R interval of 0.09 second, and a QRS complex widened and slurred in its initial portion, duration 0.12 second. The tracing is not reproduced since it is of the type shown in Fig. 1, Case 1. There is a certain amount of doubt as to the presence of cardiovascular disease in this patient. The blood pressure varies from 120/75 to 165/90 mm. There has been no progression in his symptoms. He is leading a fairly normal life without discomfort. The heart is "possibly slightly enlarged to the left." There are occasional extrasystoles.

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CORONARY EMBOLISM^{*†}

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EMBOLISM of a coronary artery is a very unusual occurrence. In a recent review of coronary sclerosis, Benson² stresses its rarity. The embolus may consist of air, fat, bacterial vegetations from heart valves, particles loosened from atheromatous lesions or broken-up thrombi. Only this latter type of embolus will be referred to in this paper. In most cases on record the source of such an embolus was either a mural thrombus in the sinus of Valsalva or ascending aorta, or vegetations from the aortic or the mitral valve. My purpose is to relate three instances of coronary embolism as proved by autopsy, and to review critically the literature of coronary embolism. Special attention is given to the source of the embolus, to its mechanism and to the type of death, whether occurring slowly or suddenly.

HISTORICAL

Virehow³¹ in 1856 was the first to describe coronary embolism. In a very short article on emboli in blood vessels, he referred to a female patient, twenty-seven years old, revealing at autopsy a recent endocarditis of the mitral valve. On gross inspection of the heart, emboli were noted in the coronary arteries. No reference is made as to whether the patient died suddenly.

Hammer¹⁰ in 1878 reported a case of coronary thrombosis in a thirty-four-year-old male. From his description, however, it is more likely that the lesion in question was an embolus rather than a thrombus. There also was endocarditis of the aortic valve and a thrombus in the sinus of Valsalva corresponding to the right aortic cusp. The author did not mention the type of endocarditis. The patient apparently survived the embolism for eighteen hours.

Huber¹² in 1882 described an embolus in the descending branch of the left coronary artery in a sixty-four-year-old male. The patient died suddenly. The origin of the embolus was a thrombus in the main stem of the left coronary artery. Three similar cases were mentioned, but no details given.

Korezyński¹⁷ in 1887 referred to a recent embolus in the circumflex branch of the left coronary artery. He did not definitely state the source of the embolus, but mentioned a chronic endocarditis of the aortic

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valve. The patient was a female, thirty-eight years old, who died suddenly.

Hektoen¹¹ in 1892 noted an embolus in the left coronary artery at the site of its division into the descending and circumflex branches in a thirty-two-year-old male who had died suddenly. The source of the embolus was a parietal thrombus in the aorta.

Oestreich,²⁴ in the same year, described an embolus occluding the mouth of the left coronary artery. This case will be referred to later.

Rolleston²⁷ in 1896 mentioned the case of a seventeen-year-old male patient dying suddenly. An embolus was found in the descending branch of the left coronary artery, the source of which was a ventricular thrombus.

Chiari⁶ in 1897 referred to an embolus in the main left coronary artery in a thirty-two-year-old man. The source of the embolus was apparently a thrombus occurring on a small atheromatous ulcer in the aorta. An organizing thrombus was found occluding the orifice of the main right coronary artery. The patient had died suddenly.

Welch³² in 1899 described the sudden death of a thirty-six-year-old female. There was an embolus in the descending branch of the left coronary artery. He did not mention specifically the source of the embolus, but stated that there were old and recent vegetations on the mitral valve and fresh vegetations on the aortic valve.

Thorel³⁰ in 1903 held thromboendocarditic excrescences in the sinus of Valsalva corresponding to the left aortic cusp responsible for an embolus in the coronary artery. No reference was made to the exact location of the embolus or to the type of death.

MacCallum²¹ in 1905 reported a case of a middle-aged male who died suddenly. There was a vegetative endocarditis of the mitral valve and an embolus in the mouth of the left coronary artery.

Lamb¹⁹ in 1913 described, in a case of vegetative and ulcerating aortic endocarditis, vegetations plugging the mouth of the left coronary artery. The patient, a male thirty-five years old, died suddenly.

Gallaverdin and Dufourt⁸ in 1913 mentioned an embolus in the descending branch of the left coronary artery in a male patient sixty-three years old. The death did not occur suddenly. There was an old myocardial scar with mural thrombi. Also, without giving detailed references, they mention a case of Leclerc in which an embolus was found in the circumflex branch of the left coronary artery in a patient who likewise had an infectious endocarditis.

Kaufmann¹⁵ in 1922 mentioned a case of sudden death in a male patient thirty-five years of age. There was an embolus in the descending branch of the left coronary artery. A thrombus was found on the aortic intima just above the posterior cusp of the aortic valve.

Kusnetzowsky¹⁸ in 1923 found an aneurysm of the heart in a fourteen-year-old boy. Though the author mentioned a coronary embolus as a

possible cause of the aneurysm, no definite statements were found in this report to justify the assumption of an embolus. There was no statement as to whether death was protracted or sudden.

Rindfleisch²⁶ in 1924 found an aneurysm in a thirty-six-year-old male. He believed that an embolus in the coronary artery had produced the aneurysm. The embolus, however, was not described in this paper. Yet the author stated that it would be difficult to say where the embolus originated. This was not a case of sudden death.

Benson and Hunter⁴ in 1925 attributed fourteen instances of coronary occlusion to embolism but gave no details.

Wolff and White³⁴ in 1926 described three instances in each of which the source of embolus was an endocarditis. The ages were twenty-three, thirty-one and forty-six years respectively. In two of these cases death occurred suddenly, while in one no reference was made as to the type of death. They also reported a fourth case which will be discussed later.

Murray²³ in 1926 referred to a young man dying unexpectedly. One of the coronary arteries was plugged by an embolus. The author did not designate which coronary artery was involved. Vegetations were found on the aortic intima close to the orifice of one of the coronary openings.

Bopp⁵ in 1926, in an article entitled "A Report of a Case of Coronary Embolism With Rupture of the Heart," described a sclerosis of the left coronary artery with obstruction of the lumen, apparently produced by a calcareous mass. In his description there is nothing to indicate the presence of a possible source of an embolus in the coronary artery. The patient was forty-six years old, showed a rupture of the heart, and died suddenly.

Table I is included to summarize only those cases of coronary embolism which were proved as such at the autopsy and which were reported with more details.

Table I indicates that death in the majority of patients occurred suddenly. It also shows that the left coronary is the most commonly involved artery, especially its descending branch.

As to the general views expressed on this subject, it should be mentioned that Marie²² in 1896 stated that there is only one unquestionable case of coronary embolus on record. This is the case of Virchow.³¹ Welch³² in 1899 said that coronary embolism is far less frequent than thrombosis, but Marie's²² position that scarcely more than one or two of the reported cases of coronary embolism are free from criticism seemed too extreme. Gallavardin and Dufourt⁸ in 1913 mentioned that only three or four cases of coronary embolism are on record. Allbutt¹ in 1915 stated that embolism in the coronary vessels is probably a very rare event. Kaufmann,¹⁵ Dietrich,⁷ Jores,¹³ and Kirch¹⁶ also stressed the rarity of coronary embolism.

It might be interesting to mention in this connection that Romberg²⁸

in 1925 discussed embolism and thrombosis of the coronary arteries in the same chapter, without especial differentiation between the frequency of the occurrence of each disease.

This survey of the literature indicates the rarity of coronary embolism, at least if one judges from the scanty case reports. Several of the re-

TABLE I

AUTHOR	YEAR OF PUBLICATION	AGE	SEX	SOURCE OF CORONARY EMBOLUS	BRANCH OF CORONARY ARTERY INVOLVED	TYPE OF DEATH
Virchow	1856	27	Female	Recent endocarditis	Several branches	?
Huber	1882	64	Male	Thrombus in main left coronary artery	Descending branch of left coronary artery	Sudden
Korezyński	1887	38	Female	Possibly an endocarditis	Descending branch of left coronary artery	Sudden
Hektoen	1892	32	Male	Parietal thrombus of aorta	Left coronary artery at site of division into the descending and circumflex branches	Sudden
Rolleston	1896	17	Male	Thrombus in left ventricle	Descending branch of left coronary artery	Sudden
Chiari	1897	32	Male	Parietal thrombus of aorta	Main stem of left coronary artery	Sudden
Welch	1899	36	Female	Recent endocarditis	Descending branch of left coronary artery	Sudden
MacCallum	1905	Past middle age	Male	Recent endocarditis	Mouth of left coronary artery	Sudden
Lamb	1913	35	Male	Recent endocarditis	Mouth of left coronary artery	Sudden
Gallavardin and Dufourt	1913	63	Male	Ventricular thrombus	Descending branch of left coronary artery	Gradual
Kaufmann	1922	35	Male	Parietal aortic thrombus	Descending branch of left coronary artery	Sudden

ports reviewed here are apparently not convincing as examples of coronary emboli. Karsner¹⁴ stated that if the occlusion of the coronary artery is due to emboli, a source of the emboli must be indicated. If the source of the embolus is not clearly demonstrable, the case should not be accepted as a proved case of coronary embolism, not only because it is not completely explained but also because the demonstration of the source of the embolus aids materially in differentiation between thrombus

and embolus. This is the more important because the histological differentiation is very difficult and often cannot be made. Only in cases where the vessel wall is healthy is it evident that the lesion in question is an embolus rather than a thrombus.

CASE REPORTS

CASE 1.* *Clinical Findings:* The patient, a thirty-five-year-old male, was admitted to the hospital because of bronchopneumonia. The previous history was irrelevant. On the day after admission it was noted that the pneumonia was spreading and that there was auricular fibrillation. He was given digitalis and put in an oxygen tent. A few days later, the patient was quite restless and complained of pain in the right leg. Subsequently, the leg became cold from the mid-thigh down, dusky, and of a mottled blue color. The right femoral artery showed no pulsation at the inguinal ring. Gradually, the leg became mummified and amputation was advised as soon as the patient's condition improved. About three weeks after the first onset of pain in the right leg, a definite line of demarcation of the gangrene had formed, and, under ethylene anesthesia, the leg was amputated between the middle and lower third of the femur. The popliteal artery and veins were occluded. Just below the knee an abscess was encountered, which was cultured and revealed streptococci and staphylococci. The patient gradually improved after the operation and was in excellent condition. Seventeen days after the operation, without any premonitory symptoms, he died suddenly. The clinical diagnosis was resolving pneumonia; embolus in the right femoral artery, with gangrene of the leg; thrombosis of the right femoral vein, and pulmonary embolism.

Autopsy Findings: The autopsy revealed a well developed but markedly emaciated white male about thirty-five years old. The right limb had been amputated at the junction of the lower and middle thirds of the femur. The pericardial and peritoneal cavities appeared normal. Both pleural cavities, however, were partially obliterated; there were fibrous adhesions which were torn with difficulty. The aorta showed a marked diffuse arteriosclerosis with an atheromatous ulcer very close to the bifurcation. The ulcer was covered by a mural thrombus. The right femoral artery was completely occluded by an embolus. The right external and internal iliac arteries also revealed arteriosclerotic changes. The right femoral vein was completely occluded by a thrombus which extended into the right iliac vein. The heart was enlarged, weighing 400 grams. The right auricle contained an embolus which extended into the right ventricular cavity. The foramen ovale was patent. A small embolus was found in the descending branch of the left coronary artery in an area about 1 cm. from its point of origin. The intima of the coronary arteries was smooth. The remainder of the heart showed no changes. Both lungs were air containing, with the exception of the right lower lobe which was firmer than normal and which on section showed many large areas which were coarsely granular in appearance, dry and gray. There were several minute emboli in the smaller branches of the pulmonary arteries on both sides. The hilus nodes were enlarged. On section, some of them were partially calcified and showed caseous necrosis in their centers. The brain was moderately hyperemic. Multiple sections of the brain showed no pathological changes.

Histological examination of the lung revealed a characteristic organized bronchopneumonia. The smaller and larger arteries in the sections of the lung showed marked arteriosclerosis. The thrombus in the femoral vein and the embolus in the femoral artery proved to be organized. There also was an acute and chronic inflammation around the femoral vein.

*I am indebted to Dr. George Davenport for the clinical notes.

Summary: This was a case of diffuse arteriosclerosis with mural thrombi in the aorta, from which a piece had broken loose and lodged in the right femoral artery, causing gangrene of the leg. The marked arteriosclerosis of the femoral artery, the pressure of the embolus upon the femoral vein, and also the inflammatory changes close to the vein might have been responsible for the thrombosis of the femoral vein. Pieces of the thrombi had broken loose and formed emboli which lodged in small branches of the pulmonary artery and also in the right auricle, partially extending into the right ventricle. There was a patent foramen ovale through which an embolus must have entered the left heart and lodged in the descending branch of the left coronary artery. The patient died suddenly.

CASE 2.* Clinical Findings: The patient, seventy years old, male, was admitted to the hospital because of attacks of pain typical of angina pectoris. The physical examination revealed weak but regular heart sounds. The heart was enlarged on percussion. The liver was also enlarged. A pericardial friction rub was noted. A few days after admission to the hospital, auricular fibrillation developed. The patient gradually improved, but on the sixth day of his hospitalization his pulse suddenly became weak and irregular. Cheyne-Stokes breathing and marked cyanosis developed, and he died within a few minutes. The clinical diagnosis was coronary thrombosis and myocardial infarction.

Autopsy Findings: The body was that of a well developed, slightly emaciated white male about seventy years old. There was a diffuse arteriosclerosis, with marked coronary sclerosis. The heart was hypertrophied and dilated, weighing 635 grams. There was an arteriosclerotic occlusion of the ramus marginis obtusi of the left coronary artery and a recent infarct in the lateroposterior wall of the left ventricle. An acute fibrinous pericarditis was found in the corresponding area of the pericardium. The circumflex branch of the right coronary artery in an area about 1 cm. from its mouth, showed an atheromatous ulcer and a small mural thrombus. In the region where the posterior descending branch comes off from the right circumflex, there was an embolus, about 1 cm. in length, completely occluding the lumen of the right circumflex branch. The autopsy further revealed chronic passive hyperemia of the visceral organs but otherwise no changes of note.

Histological Examination: Sections of the circumflex branch of the right coronary artery which contained the thrombus showed a typical atheromatous ulcer. The thrombus revealed evidence of organization, while the sections which were taken from the region of the embolus showed no attempt toward organization.

Summary: This was a case of marked arteriosclerosis, coronary sclerosis, and coronary thrombosis with myocardial infarction. The thrombus, located in the proximal portion of the circumflex branch of the right coronary artery, showed evidence of organization and did not completely occlude the lumen. To judge from the appearance of the thrombus and also from the history, it is likely that the thrombus was about six days old. A piece of the thrombus had broken loose and formed the embolus which had lodged in the region where the posterior descending branch comes off the right circumflex branch. The patient died suddenly as a result of the coronary embolism.

*I am indebted to Dr. Leon Bloch for the clinical notes.

CASE 3.—This was a private case which was not admitted to the hospital.* The patient, a male seventy-two years old, had a history over a period of seventeen years typical of angina pectoris. He had been under the constant care of a physician during the last six years of life, having more or less constant attacks of angina pectoris and attacks of pain in the legs. After a quiescent period of some duration he again had a sudden severe attack which was diagnosed clinically as coronary thrombosis. He improved, however, and was well for about a year when he had another similar, very severe attack. He recovered, however, but showed signs of congestive heart failure. His heart did not seem to be enlarged. There was a slow but definite improvement. Without warning, however, he died suddenly three weeks after the last attack. The clinical diagnosis was coronary sclerosis and thrombosis, with myocardial infarction, and probable rupture of the heart.

Autopsy Findings: The body was that of a well developed and well nourished white male of about seventy years of age. Both pleural cavities contained a slightly excessive amount of fluid. The pericardial and peritoneal cavities appeared normal. The heart was enlarged, weighing 500 grams. An aneurysm in the apical portion of the left ventricle was found, as well as a diffuse myocardial fibrosis. There was a sclerosis of the coronary arteries and complete occlusion of the descending branch of the left coronary artery by an old, completely organized thrombus. The aorta revealed marked arteriosclerotic changes, with an atheromatous ulcer in the aortic wall of the sinus of Valsalva; the ulcer was covered by a thrombus. The mouth of the right coronary artery, being very close to the atheromatous ulcer, was plugged by a very recent embolus which apparently had arisen from the thrombus covering the atheromatous ulcer. The remainder of the visceral organs showed evidence of chronic passive hyperemia.

Histological examination of the aorta showed a typical atheromatous ulcer covered by an organizing thrombus. The embolus at the mouth of the right coronary artery revealed no evidence of organization.

Summary: This was a case of diffuse arteriosclerosis, with old occlusion of a main branch of the left coronary artery. The embolic occlusion of the mouth of the right coronary artery was responsible for the sudden death.

DISCUSSION

Each of the three cases showed a coronary embolus which had led to sudden death. The sources of the emboli were a venous thrombus (by patent foramen ovale) in the first instance, a mural thrombus in the coronary artery in the second instance, and a small mural thrombus covering an atheromatous ulcer in the sinus of Valsalva in the third instance.

The first case is of interest because of the unusual source of the embolus and the paradoxical embolism. I was able to find only one such case in the literature. This case was reported by Wolff and White.³⁴ These authors described a forty-three-year-old female with a carcinoma of the ovaries. The pelvic veins were thrombosed. There was a patent foramen ovale, and an embolus was found in the descending branch of the left coronary artery. The authors did not state whether the patient succumbed slowly or whether death occurred suddenly. A somewhat

*I am indebted to Dr. Solomon Strouse for his clinical records.

similar case in which the embolus, however, consisted of tumor cells was described by Thompson and Evans.²⁹ They found a primary teratoma of the testis in a patient who at autopsy also revealed a patent foramen ovale and a tumor embolus in the left coronary artery. The authors did not state which branch was involved. Emphasis was laid, in their article, upon the mechanism of paradoxical embolism. To favor the establishment of a paradoxical embolism, they believed it essential that over one-third of the pulmonary circulation be depleted by a pulmonary embolism or that the pressure in the right auricle be increased. Wittig³³ maintained that the presence of a thrombus and open foramen ovale is not enough to explain paradoxical embolism. The flow of blood from the right to the left auricle is essential. He believed that an increased pressure in the right auricle as seen in cases of emphysema or pneumonia may be responsible for the passage of blood through the foramen ovale. Our case revealed an organizing bronchopneumonia, multiple emboli in branches of the pulmonary artery, and, also, an embolus in the right auricle, extending partly to the right ventricle. These findings might easily explain an increased pressure in the right auricle and be responsible for the passage of the embolus from the right into the left auricle. It probably is purely accidental that the embolus lodged in the descending branch of the left coronary artery.

It is interesting to note that a single embolus in one branch of the coronary artery has caused sudden death. None of the other coronary branches revealed any changes. This should be emphasized in view of the fact that a complete occlusion of a branch of the coronary artery, either by arteriosclerotic plaques or by a thrombus, does not necessarily lead to sudden death. This patient was thirty-five years old, at which age collaterals of the coronary arteries apparently were not yet established sufficiently (Gross⁹). Also, the fact that the coronary arteries were normal seems to speak against the assumption of a collateral circulation. An embolus in a main branch of the coronary artery, therefore, must have shut off enough of the nutrition of the heart to be responsible for the sudden death.

The second case was typical of coronary sclerosis and thrombosis with myocardial infarction. The patient also had a mural thrombus in the circumflex branch of the right coronary artery which, however, did not completely occlude the lumen. The thrombus must have been present for some time because of its organization. The patient, therefore, could not have died of the thrombus. The death finally occurred suddenly following the embolus which had resulted from the mural thrombus. Emphasis might be laid upon the fact that both the thrombus and the embolus were found in the same branch. This shows how important it is to open the coronary arteries in such cases completely and not to stop the dissection when a thrombus is found in the proximal portion of a coronary artery. The patient died suddenly of coronary embolism.

The abruptness of the death is explained by the additional findings of the marked arteriosclerosis of other branches of the coronary artery and the old myocardial lesions.

Huber,¹² as was mentioned before, described in detail one similar case. He also referred to three other cases but without details.

The third case is very unusual. The sudden death was undoubtedly caused by the embolus which occluded the mouth of the right coronary artery. The left descending branch was plugged by an old thrombus. There are several cases reported in the literature which are somewhat similar to this one. Oestreich²⁴ reported a thirty-year-old male dying suddenly during his wedding night. There was an arteriosclerotic ulcer covered by a thrombus in the aorta at the site of the sinus of Valsalva. The mural thrombus had occluded the mouth of the right coronary artery. The thrombus also gave rise to an embolus which had lodged in the main stem of the left coronary artery. Chiari⁶ described a thrombus which had occluded the main stem of the right coronary artery. There was also a recent embolus in the main stem of the left coronary artery. The thrombus from which the embolus originated apparently occurred on the basis of an atheromatous ulcer in the sinus of Valsalva. Barth² referred to a thirty-year-old male who died suddenly. A thrombus had occluded the mouth of the right coronary artery. The thrombus occurred on the basis of an atheromatous ulcer of the aorta situated close to the opening of the right coronary artery.

The sudden death in the last case is easily explained in view of the fact that there was also an old thrombus in the descending branch of the left coronary artery. The recent embolus which had occluded the mouth of the right coronary artery, took its origin, as in the three last mentioned reports, from an atheromatous ulcer in the ascending aorta.

Why the coronary arteries are so rarely the seat of true embolism is very difficult to explain. Marie²³ believed that the marked difference of the calibers of the aorta and the coronary arteries is in part responsible for the rarity of coronary embolism. Powell²⁵ stated that the situation of the coronary vessels at the commencement of the aorta, the right angle at which they leave the vessel and the bulk and impetuosity of the blood current at this portion are all conditions unfavorable to the passage of a clot into these small sized arteries. This opinion is also shared by Benson.³ If the right angled departure of the coronary arteries were the only reason for the rarity of coronary embolus, this might explain why emboli do not more frequently lodge in the coronary vessels, but would not explain why the mouth of the coronary artery is not more frequently involved in embolism. The various eddies at the mouths of the coronary arteries as produced by systole and diastole, and also the peculiar flow into the coronary vessels during systole and diastole might explain the rare involvement by emboli of the mouths of the coronary arteries and of the vessels themselves.

SUMMARY

The literature on coronary embolism is reviewed and the rarity of such an occurrence emphasized. Cases in which the source of the embolism is not found at autopsy should not be accepted as proved cases of coronary embolism. Three cases of coronary embolism are reported. In one, the source of the embolus was a thrombus in the femoral vein; there was also a patent foramen ovale. In the second case, the source of the embolus was a mural thrombus in the right coronary artery, occurring on the basis of an atheromatous ulcer. The embolus had lodged in the distal part of this artery at the origin of the posterior descending branch. In the third instance, the source of the embolus which had occluded the mouth of the right coronary artery was a thrombus occurring on an atheromatous ulcer in the region of the sinus of Valsalva. In all three instances the patients died suddenly.

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OBSERVATIONS ON ARTERIAL BLOOD PRESSURE DURING ATTACKS OF ANGINA PECTORIS*

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THE character, intensity and distribution of the pain of angina pectoris have long been a matter of clinical study and speculation. At present, however, the phenomena taking place during the actual anginal attacks are being investigated in greater detail. Changes in the electrocardiogram have been noted during spontaneous attacks of angina pectoris,^{1, 2, 3} and during attacks produced by epinephrine⁴ or by deliberate effort.⁵ Frequent reference has also been made by many writers to changes in blood pressure during such attacks. Curiously enough, although such statements are very common, data concerning the blood pressure during anginal spells are very meager. The statement is frequently seen that the blood pressure during attacks is variable, that it may be unchanged or be lowered or increased. Such are the views expressed by Keefer and Resnik⁶ and by Sutton and Lueth.⁷ It is noticeable that, with few exceptions, the cases that are published in detail show a higher level of blood pressure during pain than when the attack has subsided. The four cases reported by Lewis⁸ and the eight by Burgess⁹ all showed higher levels of blood pressure during spontaneous attacks of angina than those found in the same patients when free from pain. Only two of the thirty patients studied by Wood and Wolferth⁵ showed a fall in blood pressure during attacks of angina. Allbutt¹⁰ also mentions a similar case with a fall in blood pressure. It is the purpose of this study to record additional observations on the blood pressure during attacks of angina pectoris and to urge others to make similar notations.

The opportunities to make examinations of the blood pressure during attacks of angina are neither numerous nor conducive to prolonged study. The physician under such circumstances feels the need to bring the attack to an end and necessarily uses medication which of itself diminishes the blood pressure. It is therefore more difficult to draw the proper conclusions concerning the blood pressure changes than it would be if we dared to await the spontaneous disappearance of the attacks. There is much of an inferential character, however, to be obtained from these experiences. We have had the opportunity during the past decade or so to obtain readings of the blood pressure during spontaneous attacks of anginal pain in twenty-three patients (Table I). Of the accuracy of the diagnosis in these cases there is very little doubt. No attempt has been made to correlate the time of disappearance of the

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pain and the change in blood pressure. This has been done in small groups of patients by Lewis⁸ and Burgess.⁹ In seven of our patients, the level of the blood pressure preceding the attack was known. In some of these, the readings were actually obtained a few minutes before the attack. In most of the cases, the attack was brought to an end by the use of nitroglycerin. In three, however, the pain was allowed to subside spontaneously, and blood pressure measurements were therefore obtained

TABLE I

OBSERVATIONS ON ARTERIAL BLOOD PRESSURE IN SUBJECTS WITH ANGINA PECTORIS

SUB- JECT	SEX	AGE	ARTERIAL BLOOD PRESSURE					NITROGLYCERIN ADMINISTERED
			BEFORE ATTACK		DURING ATTACK	AFTER ATTACK		
			READING	INTERVAL BEFORE PAIN		READING	INTERVAL AFTER PAIN	
		YEARS	MM. HG		MM. HG	MM. HG	MINUTES	
R. B.	F	33	140/90	Few minutes	180/20	140/90	6	Yes
A. R.	F	50	110/70	Few minutes	164/94	132/88	6	Yes
R. W.	F	65			170/85	155/85	3	Yes
M. W.	M	53			138/82	98/76	11	Yes
S. S.	F	60			240/140	210/120	4	Yes
M. S.	M	62			190/90	170/85	3	Yes
H. R.	M	56			172/110	154/95	5	Yes
L. H.	F	64	160/90	10 minutes ±	230/140	165/95	6	Yes
J. G.	M	50			154/90	96/40	10	Yes
M. G.	M	62			196/110	152/90	4	No
S. C.	M	54			230/120	204/108	5	No
M. L.	M	68			210/110	130/80	300	Yes
M. H.	M	68			215/130	150/100	3	Yes
T. G.	M	62			210/110	140/80		
S. F.	M	45			140/80	108/78	3	Yes
F. B.	M	60			160/108	115/75	15	Yes
H. B.	M	68			210/145	195/120	5	Yes
P. A.	M	62	140/100	10 minutes ±	200/102	126/92	10	Yes
M. C.	F	65	170-190	During pre- vious months	210/94	190/90	4	Yes
			70 70					
A. G.*	M	31			165/90	140/90	4	Yes
B. P.†	M	70			204/80	168/64	10	Yes
E. C.‡	F	28	112/80	Few minutes	148/98	114/90	5	No
F. R.‡	M	15	130-140	Few hours	210/90	140/50	60	Yes
			50 40					

*Had thyrotoxicosis in addition to angina pectoris.

†Had syphilitic aortic insufficiency in addition to angina pectoris.

‡Had rheumatic aortic stenosis and insufficiency in addition to angina pectoris.

uninfluenced by the use of vasodilator drugs. In not a single instance did the blood pressure level fail to be higher during pain than after the pain had subsided, or than before the attack had started in those instances where earlier readings were available.

The obvious criticism may be raised that the blood pressure would have to be lowered after the use of vasodilator drugs. In seven of the patients, however, it was known that the level to which the pressure returned was the one customarily found in that same patient when free from pain. It is most significant that in no instance was the pressure

during anginal pain lower than at other times. This point deserves particular attention in the light of the statement frequently made in medical writings that the blood pressure may fall during anginal attacks.^{11, 12} We believe that such an occurrence must be very rare. When a fall in blood pressure takes place, one may reasonably suspect either that an attack of coronary thrombosis is occurring or that the pain is not anginal in character. A reconsideration of four cases published by one of us¹² ten years ago well illustrates the difficulties in this problem. Of these four cases, the one which showed a fall in blood pressure undoubtedly had a coronary occlusion. A review of all the clinical data in this case (fever, leucocytosis, pulmonary edema and sudden death) in the light of our present knowledge makes this diagnosis certain. Another patient with no change in blood pressure had apical pain accompanying hypertension and only developed the typical substernal pain of angina pectoris some years later. The remaining two showed the customary rise in blood pressure during attacks.

The question may readily be asked whether the pain of angina pectoris does not of itself produce the elevation in blood pressure. We have had the unusual opportunity of observing a patient with angina pectoris during two different attacks of severe renal colic. Two hypodermic injections of 15 mg. of morphine were required to bring relief in both these attacks. During the height of the pain there was no anginal discomfort and the blood pressure remained unchanged. Numerous readings during the course of nine years were available in this case. The systolic pressure ranged between 120 and 140 mm. Hg. and the diastolic pressure between 70 and 80 mm. Hg. At the height of the pain from renal colic on one occasion the readings were 140 mm. Hg systolic and 80 mm. Hg diastolic with a pulse rate of 68 per minute; and on the other occasion they were 120 mm. Hg systolic and 80 mm. Hg diastolic with a pulse rate of 62 per minute. We cannot therefore accept the contention that the pain of angina pectoris is the cause of the elevation in blood pressure. On the other hand, the almost constant association of rise in blood pressure with anginal pain makes one suspect that the two are related. Both may be concomitant results of a third unknown influence or the elevation in pressure may actually produce the pain. The fact that in the subsidence of the attack, pressure levels need not go hand in hand with the disappearance of pain^{8, 9} does not dismiss the possibility that the onset of the attack was actually produced by the increased pressure. It would be interesting and important to ascertain whether attacks can be precipitated by other methods of elevating pressure and whether the induction of attacks can be inhibited by preventing a rise in pressure.

SUMMARY

Blood pressure readings were obtained during spontaneous attacks of angina pectoris in twenty-three patients. In seven, the previous blood

pressure readings were known. In three, the attacks were allowed to end spontaneously, and in twenty relief was obtained by administering nitroglycerin.

In every instance the level of the systolic pressure was distinctly higher during pain than when the patient was free from pain. Although this may not be an invariable relationship, this study and a survey of the cases recently reported leads one to the conclusion that a failure of the blood pressure to rise in anginal attacks is rare.

Evidence is presented to show that in patients with angina pectoris, pain alone, e. g., that of renal colic, neither produces an elevation in blood pressure nor brings on an attack of angina.

Although we suspect that a temporary elevation in blood pressure is an important factor in the production of anginal attacks and may even be a necessary immediate cause of the attack, a final decision as to this relationship will require further investigation.

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THE OCCURRENCE OF HEART-BLOCK IN CORONARY ARTERY THROMBOSIS*

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THE occurrence of heart-block during the course of an acute coronary artery thrombosis is rare. The case to be reported, which has been studied in great detail with frequent serial electrocardiograms, revealed an early complete heart-block, which in a retrograde fashion went through the stages of partial heart-block, gradually returning to normal sinus rhythm, with complete recovery.

Acute coronary artery thrombosis usually occurs in individuals with a normal cardiac rhythm and in the majority of cases the rhythm remains regular. However, various arrhythmias can occur with the onset, and during the early stages of an acute coronary closure. The frequency with which disturbances in rhythm may be detected will depend largely upon how often the patient is examined, since many of the irregularities are transient and often cause few if any symptoms.

Premature contractions, both ventricular and auricular, are observed during the early stages of an attack and are of little or no significance. Paroxysmal auricular fibrillation occurs more frequently. Levine¹ observed it in 34 instances of his series of 145 cases. He did not find that this arrhythmia materially altered the prognosis of the case. Occasionally permanent auricular fibrillation remains. Auricular flutter is rarely seen, and in one case personally observed, the patient recovered. A more uncommon but important disturbance in rhythm is the development of paroxysmal ventricular tachycardia. This condition has been well described by Herrmann,² Robinson,³ and Levine,⁴ and Levine, Stevens, and Fulton.⁵ The prompt recognition of this disturbance and institution of proper therapy may prove life saving.

Complete A-V dissociation during an attack of acute coronary artery thrombosis can occur and has been observed. Levine¹ observed it only twice in his series of 145 cases, an incidence of 1.37 per cent. Both cases proved fatal. One of the earliest reports of transient complete heart-block in coronary thrombosis with recovery was that of Frothingham⁶ in 1927.

The presence of complete heart-block during the early stage of a coronary closure has not been adequately explained. A careful study of the case to be reported together with an analysis of the cases of heart-block in coronary thrombosis described in the literature furnishes a key to the explanation for its occurrence.

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While heart-block in coronary closure is uncommon, it is even more rare to observe all of its stages in one individual in whom recovery has taken place. The report of such a condition with frequent serial electrocardiograms is presented.

CASE REPORT

A. S., B. I. H. No. 44517, male, aged forty-six years, walked into the out-patient department of the Beth Israel Hospital, and presented the following history: Two days previously, while walking home from work, he suddenly experienced a burning sensation in the region of the lower sternum and epigastrium. He continued to walk and when he reached his home he vomited profusely and broke out into a cold

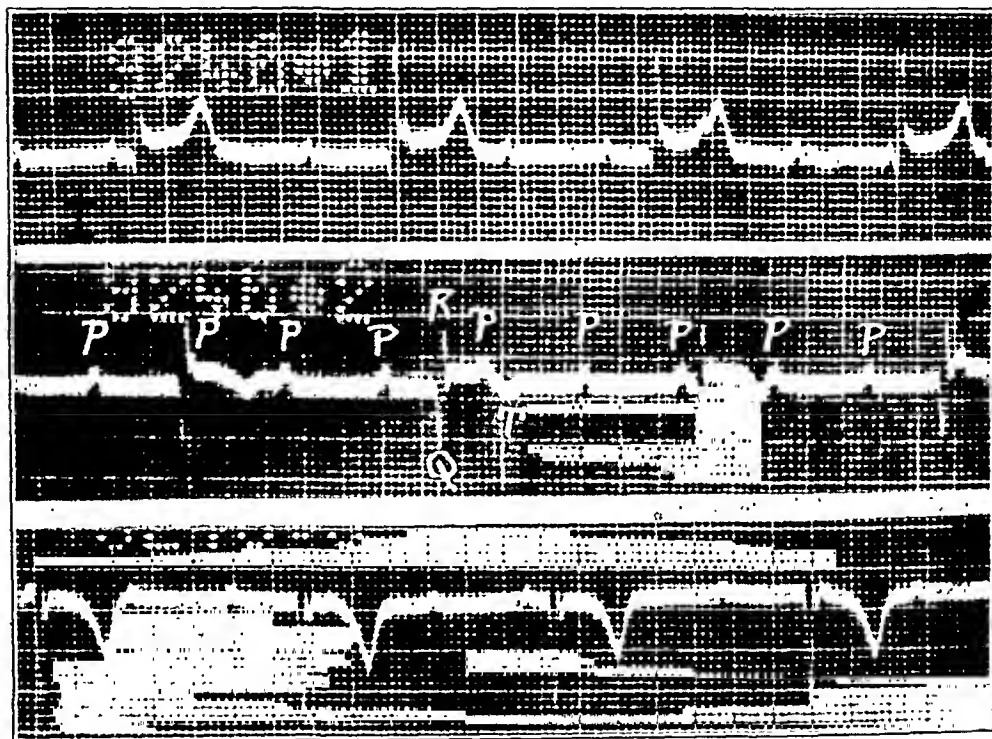


Fig. 1.—Electrocardiogram taken first day, about forty-eight hours after onset of attack. Complete auriculoventricular dissociation. Auricular rate 117, ventricular rate 45 per minute. T_2 slightly inverted. T_3 deeply inverted with cove-plane shape. Deep Q-waves in Leads II and III.

sweat. He slept poorly that night because of pain and burning in the epigastrium which was almost constant. There was difficulty in breathing. The pain was intensified when he was lying on the left side, and he perspired profusely during the night. He remained at home the next day and complained of intermittent burning and pain in the epigastrium and lower chest, which continued through the night but was less severe than the night before. He then walked about one mile from his home to the clinic. The pain became worse on walking, and for the first time it was felt in the region of the left shoulder. Physical examination revealed signs of an extensive pericarditis. The heart rate was 72 per minute and there were occasional premature beats. He was immediately sent into the hospital. He protested and maintained that he had only "stomach trouble" and did not require hospitalization. When examined in the ward, he showed the following: Temperature 100.2° , pulse 50, respiration 24. He was sitting up in bed and did not appear acutely ill.

He was only slightly dyspneic and perspired moderately. There was slight cyanosis of the lips, and he complained only of very slight pain behind the lower sternum. Pressure over the styloid process (Libman's test) indicated an individual who was markedly hyposensitive to pain stimuli. The apex beat was not visible nor palpable, but the heart was slightly enlarged to the left on percussion. The rhythm was regular and the rate 50 per minute. A typical loud, leathery to-and-fro pericardial friction rub was heard over almost the entire precordial area. The first heart sound was impure and at times was heard with a varying degree of intensity due to the varying time relationship between auricular and ventricular contraction as occurs in complete heart-block. A third sound, distinctly grating in quality, was constantly heard in about the middle of each long diastolic pause. It was at first thought that it was either an auricular or a pericardial sound. The final impression was that

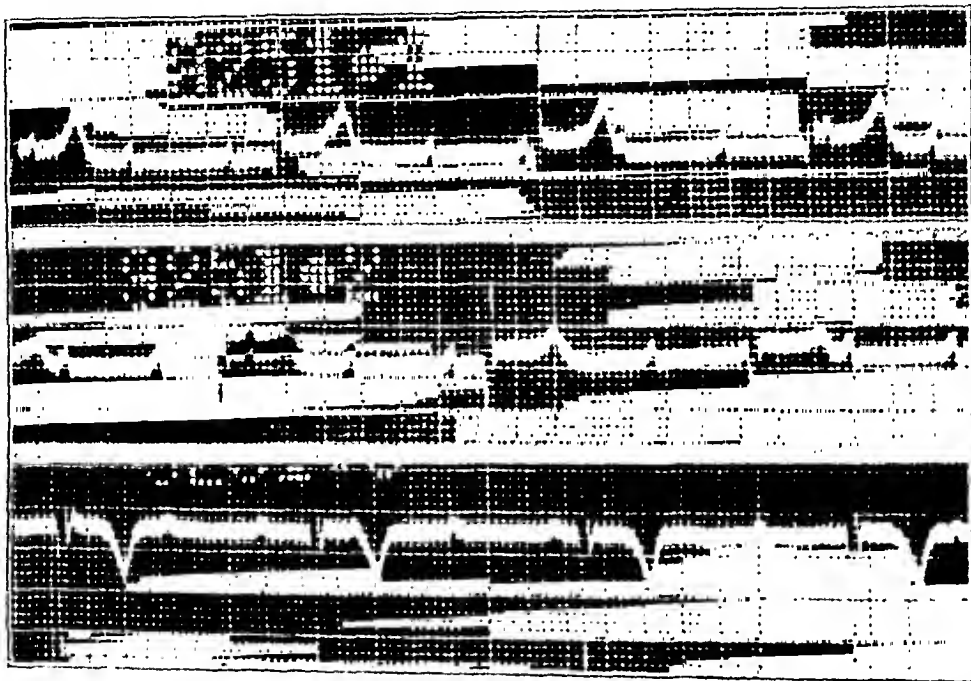


Fig. 2.—Third day. Complete A-V dissociation. Elevated R-T segment in Leads I and II. Deep Q_2 and Q_3 . T_2 inverted and cove-plane.

this peculiar sound was of pericardial origin, produced by the visceral and parietal layers of the pericardium coming in contact during the diastolic "ballooning" out of the ventricles. This peculiar sound was heard only during the period of complete heart-block. The lower edge of the liver was 5 cm. below the costal margin. The history and the peculiar clinical findings suggested the diagnosis of acute coronary artery occlusion, probably involving the right coronary artery, with complete A-V dissociation. The clinical diagnosis of right coronary artery occlusion was made because of the enlargement of the liver and the associated heart-block. Electrocardiograms (Figs. 1 and 2), the first of which was taken approximately forty-eight hours after the onset of the attack, confirmed the clinical diagnosis and showed a complete A-V dissociation with evidence of acute myocardial injury. There was elevation of the R-T segment in Leads I and II and deep cove-plane inversion of the T waves in Lead III.

During the first two days in the hospital he complained only of slight retrosternal pain and was given morphine sulphate, grains $\frac{1}{4}$ (0.015 gm.) three times. He was remarkably free of symptoms during the remainder of his hospital stay of fifty-eight days. The temperature which on admission was 100.2° , rose to 102° on the

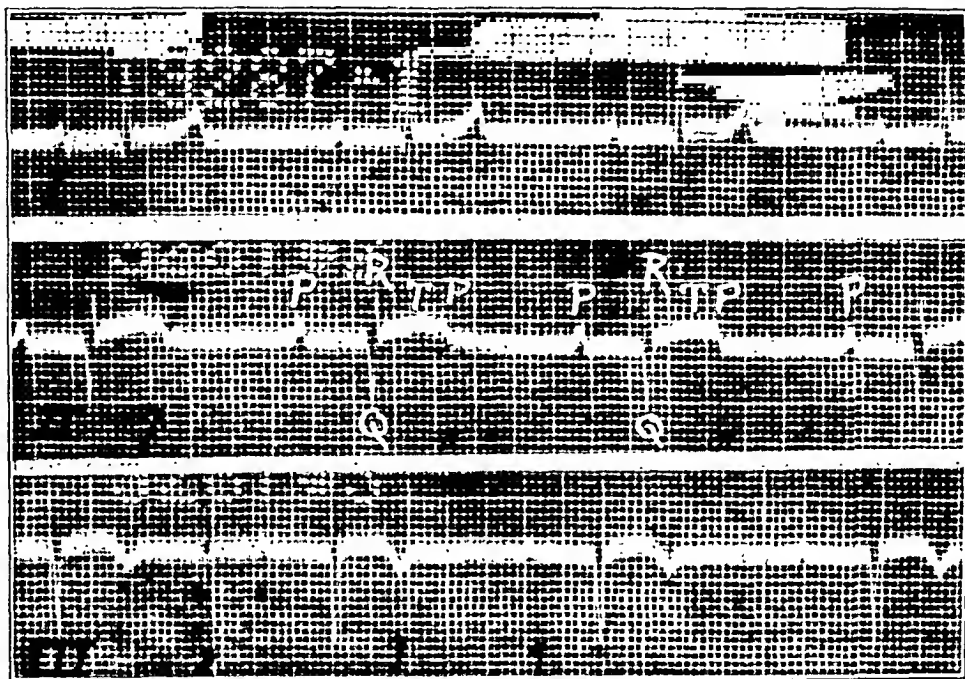


Fig. 3.—Seventh day. Two-to-one block. R-T segment Lead I almost isoelectric. T_s less inverted.

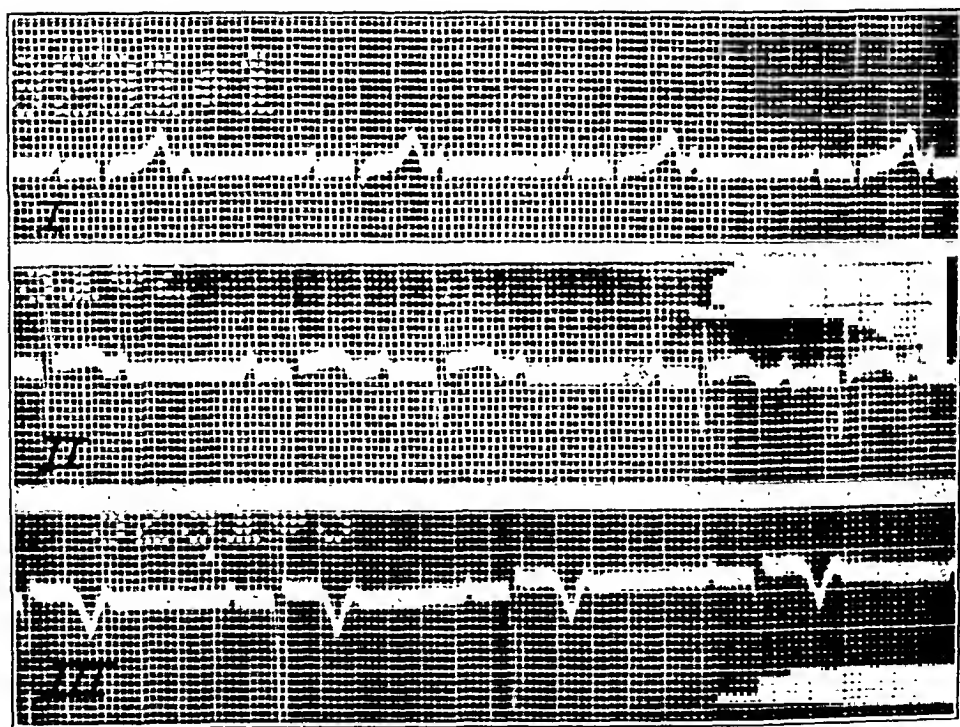


Fig. 4.—Eighth day. Two-to-one block in Lead I. Varying two-to-one and one-to-one conduction in Lead II. Two-to-one block in Lead III.

second day and gradually declined, becoming normal on the sixth day. The white blood count on admission was 16,050 with 82 per cent polynuclear leucocytes. The sedimentation rate was 42 per cent (normal 3 to 10 per cent). The leucocytosis persisted for three weeks and the sedimentation rate became normal (5 per cent) on the twenty-seventh day. The blood pressure varied between 92 and 136 mm. of mercury systolic, and 68 to 90 mm. diastolic. The blood Wassermann and urine examinations were negative. The liver, which was at first enlarged, gradually receded and could no longer be felt after the seventh day. The complete heart-block lasted for six days. During this period, the ventricular rate (electrocardiographically) varied between 45 and 60 per minute. Clinically, the heart rate dropped as low as 42 per minute. On the seventh day, the electrocardiogram (Fig. 3) showed a two-to-one heart-block with a ventricular rate of 53 per minute, and because of this

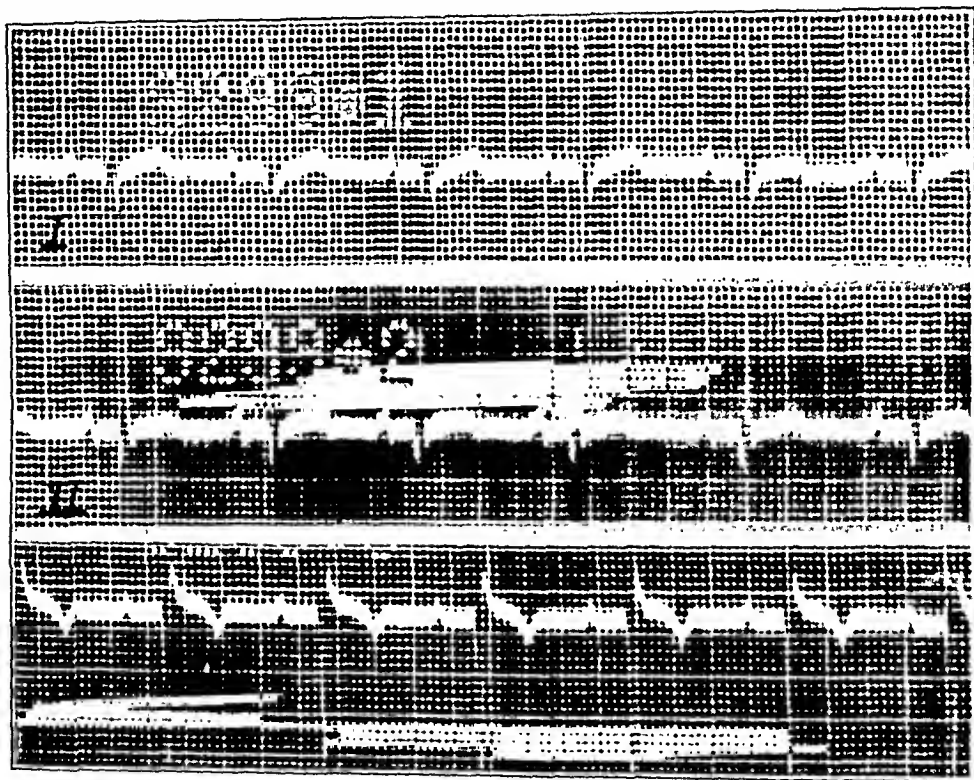


Fig. 5.—Ninth day. Normal sinus rhythm. P-R interval measures 0.22 sec.

a return to normal sinus rhythm was anticipated. The next day (eighth day) the cardiac rhythm was irregular. The electrocardiogram (Fig. 4) showed an arrhythmia due to a varying two-to-one block and one-to-one A-V conduction. The rhythm became regular the next day (ninth day). Electrocardiogram (Fig. 5) showed a normal sinus rhythm with a rate of 82 per minute. The P-R interval measured 0.22 second, the last remaining evidence of the heart-block. On the next day (tenth day) the electrocardiogram showed a normal P-R interval and normal sinus rhythm remained permanently established. The pericardial friction rub was heard distinctly for fifteen days.

Figs. 6 and 7 show single complexes of serial electrocardiograms taken from the day of admission until six months later. They show at first the elevated R-T segment in Leads I and II and deep cove-plane inversion of T_3 . The R-T interval in Leads I and II gradually became isoelectric with inversion of the T-waves in Lead II and lesser inversion of T_3 . The T-waves in Lead I

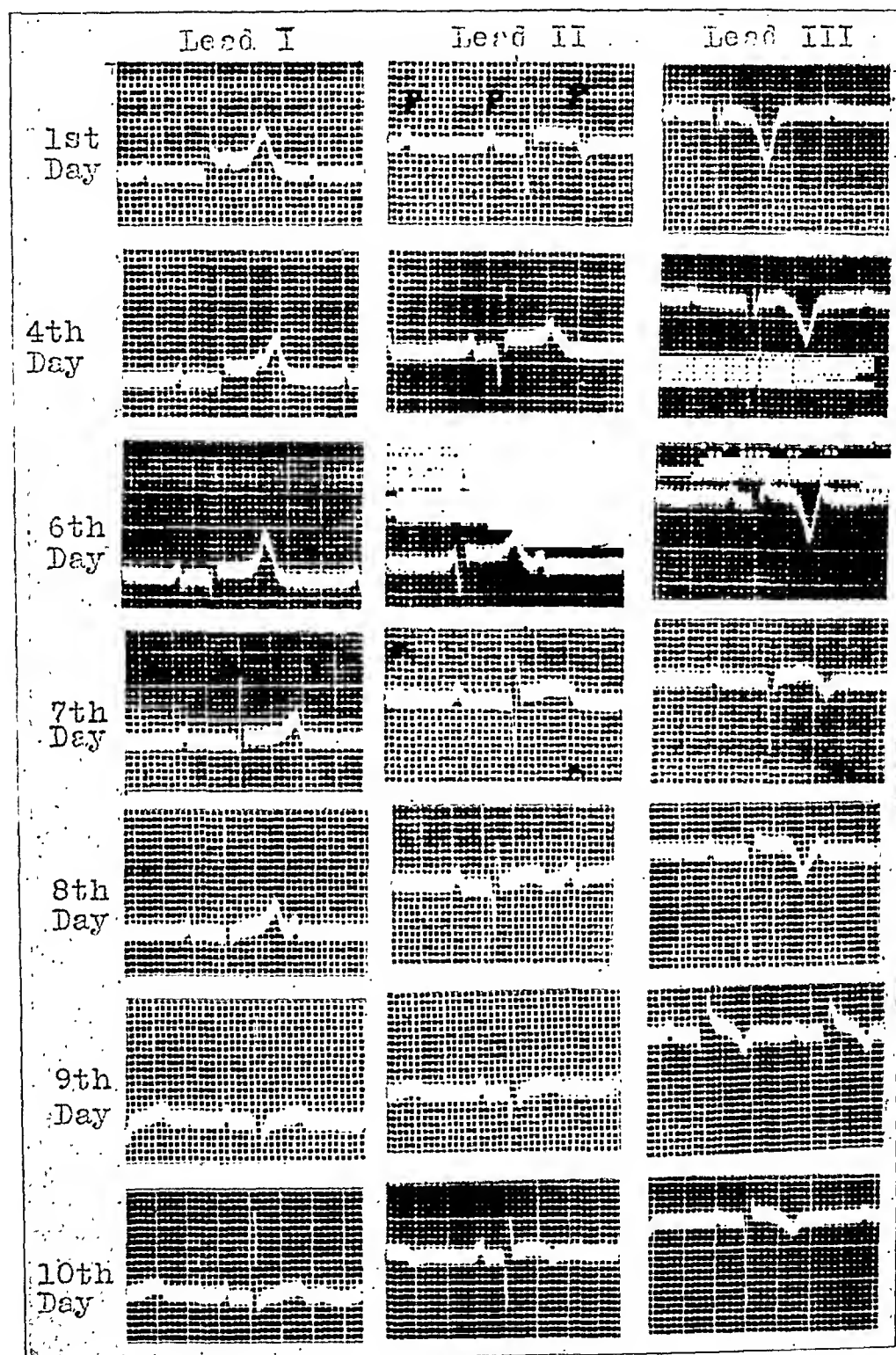


Fig. 6.—Serial electrocardiograms of single complexes from the three conventional leads from first to tenth day, showing successive electrocardiographic changes following coronary occlusion.

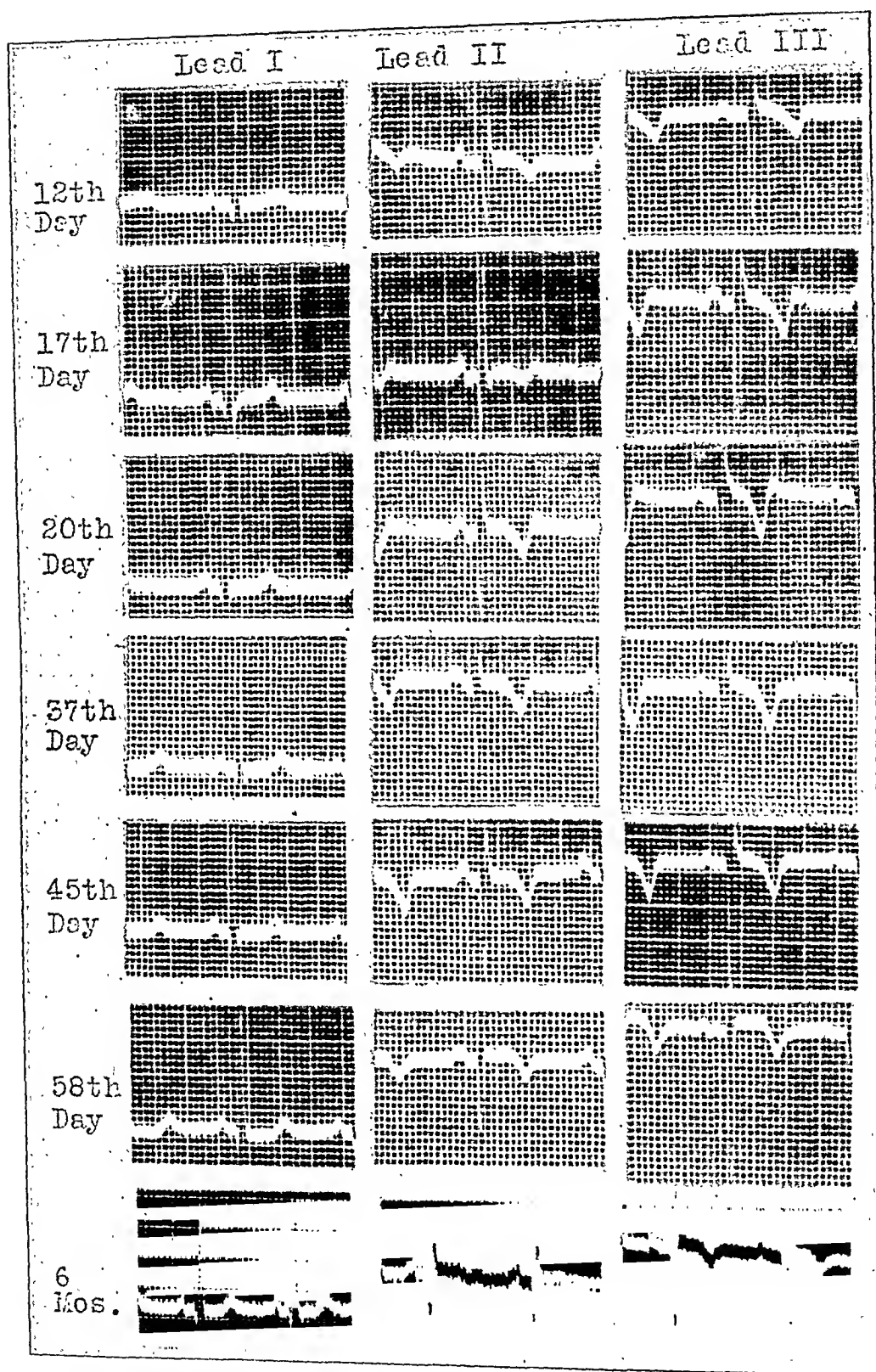


Fig. 7.—Serial electrocardiograms of single complexes from the three conventional leads from twelfth day to six months, showing successive electrocardiographic changes following coronary occlusion.

never became inverted. All of the electrocardiograms showed deep Q-waves in Leads II and III. The teleroentgenogram showed slight enlargement of the left ventricle. After the patient was discharged from the hospital he was not seen for five months. He then stated that for the preceding four months he had been working daily pressing shirts eight to nine hours a day, and felt perfectly well. Blood pressure was 180/110 mm. The heart was slightly enlarged to the left. The rhythm was regular and the rate 80 per minute. The heart sounds at the apex were of good quality, and the second aortic sound was moderately accentuated. Both lungs were clear and the liver was not palpable. The electrocardiogram (Fig. 8) now showed very little evidence of previous cardiac damage. It is significant to note that the Q-waves in Leads II and III were still deep. On the basis of the enlargement of the left ventricle and elevated blood pressure, it is assumed that this patient had a

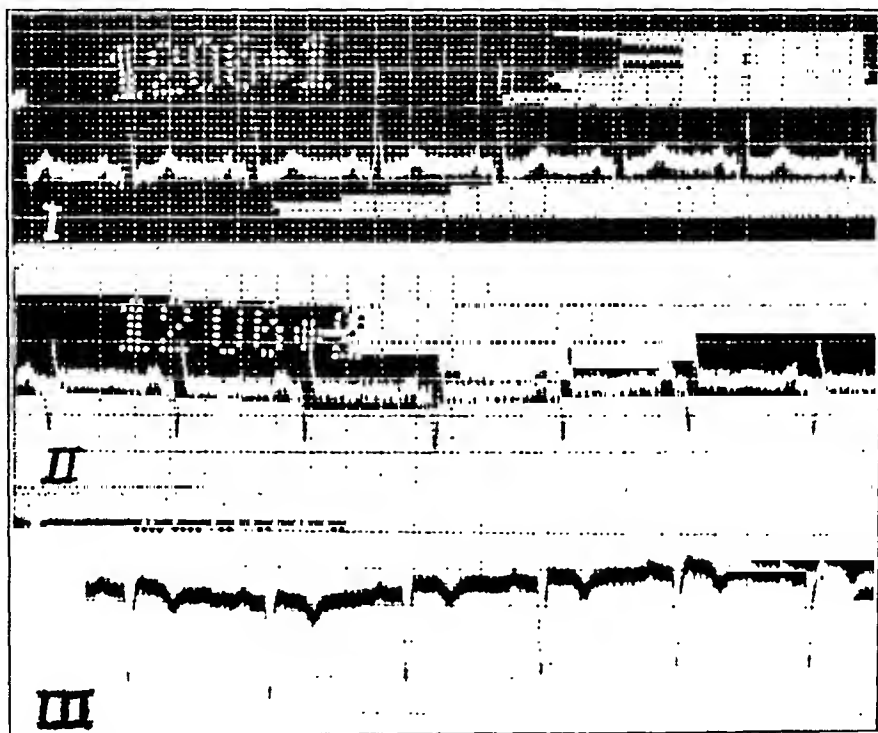


Fig. 8.—Electrocardiogram taken six months after the acute attack. Q_2 and Q_3 are still deeply inverted. T_2 slightly upright and T_3 inverted.

hypertension for some time and the first evidence of vascular disease was the occurrence of an acute coronary artery occlusion.

DISCUSSION

In many cases of coronary artery thrombosis one can, from the electrocardiograms, determine whether the occlusion involves the left or the right coronary artery, as was first shown by Parkinson and Bedford⁷ in 1928. They carefully described the successive changes in the electrocardiogram following cardiac infarction and divided the curves into two main groups: type T_1 and type T_3 . A definite sequence of changes in the R-T segment and T-waves occurs. The initial change is an elevation of the R-T segment from the isoelectric level followed later by an inversion of the T-waves in Lead I or III, but never in both, and a lesser

degree of inversion in Lead II. Curves taken a few weeks after the acute injury usually conform to one of the two main types, as evidenced by the T-wave inversions. Thus, inversion of the T-waves in Leads I and II occurs in type T_1 , indicating an occlusion of the left coronary artery, and conversely inversion of the T-waves in Leads II and III is found where the thrombosis involves the right coronary artery. The T-waves can subsequently return to a complete normal. Often an inverted T-wave in Lead III may be the only residual evidence of a previous infarction. This, plus the deep Q-waves in Leads II and III, is present in the case reported. Barnes and Whitten⁸ in a study of the correlation of the electrocardiographic changes, the artery occluded and the resultant area of infarction, confirmed the above findings. Wilson and his co-workers⁹ recently reported a study of the electrocardiograms in 56 cases of coronary thrombosis on 17 of which a postmortem examination of the heart was made. Their findings were in complete agreement with those of Barnes and Whitten. In the autopsied cases, curves showing inversion of the T-waves in Leads II and III were always associated with infarction of the area usually supplied by the right coronary artery. Crawford and his coworkers¹⁰ recently substantiated the findings of Barnes and Whitten by cauterizing definite areas of the heart muscle in cats. They produced typical type T_1 and T_3 changes in the electrocardiogram.

According to these criteria, the case reported here would fall into type T_3 , indicating an occlusion of the right coronary artery with resultant myocardial infarction. Although the R-T segment was elevated above the isoelectric level in Lead I in the beginning, the T-waves in Lead I never became inverted. The deep cove-plane inversion of T_3 at the onset, gradually becoming less inverted, and the subsequent development of inverted T-waves in Lead II (Figs. 6 and 7) place these curves in type T_3 .

Transient heart-block in coronary artery occlusion is probably due to a disturbance of the circulation to the auriculoventricular node. The A-V node receives its blood supply from the right coronary artery in 92 per cent of the cases and from the left coronary artery in 8 per cent of the cases, depending upon which vessel crosses the "crux" of the heart posteriorly. Thus it would seem that heart-block should be more common when the occlusion occurs in the right coronary artery. This premise is borne out in the following analysis of cases of heart-block with coronary artery occlusion reported in the literature, together with the case presented.

As early as 1913, Oppenheimer and Williams¹¹ described a case of prolonged incomplete heart-block without a lesion of the bundle of His. At autopsy the posterior descending branch of the right coronary artery was found completely obstructed about 0.5 cm. from its origin as well as the descending and circumflex branches of the left coronary artery.

Histological study revealed sclerosis and marked stenosis of the artery to the A-V node. Serial sections of the bundle of His did not disclose any lesion to explain the block. They stated in conclusion that "complete heart-block without anatomic lesions in the A-V system may possibly be of neurogenic or of circulatory origin, or it may be ascribed to chemical agents, to asphyxia, or to some hindrance to the passage of impulses from the terminal arborizations of the conduction system to the ventricular musculature." Later in discussing a paper by Kugel, Oppenheimer stated that since the original observation, he had had several instances in which it seemed probable that the heart-block was due to circulatory disturbance.

Parkinson and Bedford⁷ observed one case of transient heart-block in their series of cases. The electrocardiograms of this case conformed to the typical type T₃.

Hansen¹² reported a case of complete A-V dissociation occurring on the fifth day during an acute attack of coronary artery occlusion with death a few days later. The electrocardiograms were of type T₃ with a deep Q₃. Postmortem examination was not obtained.

Sanders¹³ observed a fatal case of coronary artery thrombosis with complete heart-block and a relative ventricular tachycardia. The auricular rate was 120 and the ventricular rate 70 per minute. Electrocardiograms were of the type T₃. On postmortem examination, a thrombus was found obstructing the right coronary artery with an infarction involving the greater portion of the outer wall of the right ventricle extending to the apex and to the anterior and posterior portions of the inter-ventricular septum.

Dr. M. A. Rothschild¹⁴ has kindly furnished me with a remarkable case from his private practice. This was a man of fifty-three years who had a severe attack of precordial pain and dyspnea while riding horseback. Clinically he had suffered an attack of acute coronary artery thrombosis. The electrocardiogram showed a complete A-V dissociation with inversion of the T-waves in Leads II and III, typical type T₃. The heart-block soon disappeared and the electrocardiogram subsequently became entirely normal. Four years later he developed a second attack of coronary artery thrombosis without heart-block and died. The electrocardiogram at this time was of the type T₁. This case is very important since it furnishes an interesting experiment in the same individual. The clinical and electrocardiographic evidence during the first attack would indicate that at this time he had a thrombosis of the right coronary with heart-block, while his fatal attack was electrocardiographically a left coronary occlusion without heart-block.

Frothingham⁶ observed transient complete heart-block in a case of typical coronary closure with complete recovery. In his case also, the P-R interval was prolonged when normal sinus rhythm first appeared. The electrocardiograms conformed to type T₃.

Salley¹⁵ observed a case of coronary closure with ventricular tachycardia at the onset which could not be abolished by quinidine. The injection of atropine uncovered a complete heart-block. Electrocardiograms were of the type T_3 .

Bell and Pardce¹⁶ reported a case of coronary thrombosis with complete heart-block and recovery. The heart-block lasted eight days during which period there were numerous Stokes-Adams seizures. The electrocardiograms showed classical early and late changes with the development of inverted T-waves in Leads II and III, typical type T_3 . They believed that the sudden A-V dissociation with an eventual return to normal rhythm was due to an edema of the tissues which was later absorbed.

Schwartz¹⁷ observed four patients in whom complete heart-block developed during an acute coronary artery closure. Two of the patients died and two recovered. Stokes-Adams seizures occurred in two of the cases, one of which proved fatal. Auricular fibrillation appeared in one instance before normal sinus rhythm was established. The electrocardiograms in all four cases revealed typical type T_3 changes.

Boas¹⁸ observed a woman of fifty-nine years who developed complete heart-block about five hours after the onset of an acute coronary artery thrombosis. The patient died in less than twenty-four hours. No autopsy was obtained. The electrocardiogram showed complete A-V dissociation with inversion of the T-waves in Leads II and III, typical type T_3 .

Complete heart-block has been described in sixteen cases of acute coronary artery thrombosis (Table I). Electrocardiographic tracings were obtained in fourteen of the cases, thirteen of which conformed to type T_3 indicating occlusion of the right coronary artery and the remaining case conformed to type T_1 indicating occlusion of the left coronary artery, as was found at autopsy. Confirmation by autopsy was made in three cases; in two a thrombus was found occluding the right coronary artery and in one the left. The electrocardiographic changes as to type and the anatomical findings were in complete agreement in the autopsied cases.

The high frequency of heart-block in thrombosis of the right coronary artery focuses our attention to the course of this vessel and its branches, especially the branch supplying the A-V node. The A-V node is supplied by an artery known as the ramus septi fibrosi, which arises from the right coronary artery in 92 per cent of human hearts, and from the left coronary artery in 8 per cent. This vessel furnishes the chief blood supply to the A-V node. However, important anastomoses occur in this area. Knagel¹⁹ in 1927 called attention to an important anastomotic vessel in the annule of the human heart. He later described this vessel in greater detail.²⁰ This artery, known as the arteria anastomotica auricularis magna, is a large anastomotic vessel which arises from the

left coronary artery and is constant in occurrence and site. It was found in all of the fifty normal hearts which Kugel studied. Like the main coronary arteries and their branches, it is subject to variations which fall into three groups.

1. It forms a simple direct anastomosis between the left circumflex coronary artery or its branches and the posterior portion of the right circumflex coronary artery or its branches in the region of the A-V node. This is the most common variation, occurring in 33 of the 50 hearts examined. In this common arrangement it anastomoses freely with the main artery supplying the A-V node.

TABLE I
ELECTROCARDIOGRAPHIC EVIDENCE AND AUTOPSY FINDINGS IN CASES OF
CORONARY OCCLUSION WITH HEART-BLOCK

AUTHOR OF CASE	TYPE ELECTROCARDIOGRAPHIC CHANGES	AUTOPSY FINDINGS
1. Ball	T ₃	Not done
2. Parkinson & Bedford	T ₃	Not done
3. Hansen	T ₃	Not done
4. Rothschild	T ₃	Not done
5. Frothingham	T ₃	Not done
6. Salley	T ₃	Not done
7. Schwartz	T ₃	Not done
8. Schwartz	T ₃	Not done
9. Schwartz	T ₃	Not done
10. Schwartz	T ₃	Not done
11. Bell & Pardee	T ₃	Not done
12. Boas	T ₃	Not done
13. Sanders	T ₃	Occlusion of right coronary artery
14. Levine	T ₁	Occlusion ant. desc. branch left cor. art.
15. Oppenheimer & Williams	Not done	Occlusion of right coronary artery
16. Levine	Not done	Not done

Type T₃ is associated with inversion of the T-waves in Leads II and III, indicating right coronary artery occlusion.

Type T₁ is associated with inversion of the T-waves in Leads I and II, indicating left coronary artery occlusion.

2. It forms a simple anastomosis between the left circumflex coronary artery or its branches and the anterior portion of the right coronary artery or its branches.

3. In the greater part of its course, the vessel is represented by diffuse anastomoses between branches from the anterior portions of the left and right coronary arteries and the posterior portion of the left circumflex coronary artery.

This artery thus serves as a wide anastomotic channel between the right and left coronary arteries in the region of the A-V node. In several of the hearts which were the seat of arteriosclerotic coronary artery disease, this vessel was of unusually large caliber.

We can therefore assume that where the anastomotic artery of Kugel forms a rich, collateral blood supply to the region of the A-V node as in Group 1, heart-block either is not likely to occur or may be very transient, when the right coronary artery is occluded proximal to the branch supplying the A-V node.

However, where the collateral blood supply to the A-V node is not very rich as in the third group variation, heart-block is probably more liable to occur. In this case, occlusion of the right coronary artery, proximal to the ramus septi filiosi, would temporarily cut off the main blood supply to the node and cause sufficient ischemia to prevent some or all of the stimuli from the auricles from passing through the A-V node and into the bundle of His. Partial or complete A-V dissociation with a supraventricular type of ventricular complex would then result. The impulses producing the idioventricular rhythm arise either in the lowermost portion of the node or in the upper part of the main stem of the bundle of His. This is illustrated by the fact that in all of the electrocardiographic tracings obtained in the reported cases of heart-block in coronary artery thrombosis, the ventricular complexes are always of the supraventricular type. If the patient survives the initial shock and goes on to recovery, the collateral blood supply to the A-V node, mainly through the anastomotic artery of Kugel probably comes into play and gradually supplies sufficient blood to the region of the A-V node so that it again assumes its normal physiological function.

Géraudel²¹ has furnished anatomical evidence in support of the above explanation. He demonstrated that stenosis and partial occlusion of the artery supplying the A-V node probably explained the occurrence of partial and complete heart-block in cases where a lesion of the bundle of His or its branches could not be found. By means of serial sections, he carefully examined the entire conduction system and the circulation to the A-V node in three cases of partial and complete A-V dissociation. The A-V node, bundle of His, and its branches were entirely free from any demonstrable lesion or injury in all three instances. However, a study of the artery supplying the A-V node revealed singular findings. In one case the nodal vessel arose from the left coronary artery and was almost completely obstructed by a zone of proliferative endarteritis. In the remaining two cases the artery to the A-V node arose from the right coronary, and in both instances the vessel showed marked narrowing with almost complete obliteration just above its point of origin. It may be significant that in all three cases the stenosing lesion in the nodal artery was found just at or proximal to its point of origin from the main coronary artery. In the first case the left coronary artery crossed the "crux" of the heart and supplied the artery to the A-V node, whereas in the other two cases in which the nodal artery arose from the right coronary artery, this main vessel was found to cross the "crux." This is in accord with the studies of Gross.²²

Jelliek, Cooper, and Ophuls,²³ in 1906, described a case of Stokes-Adams syndrome occurring fourteen days before death in an individual suffering from acute epididymitis and septicemia. "Postmortem examination of the heart demonstrated anemic necrosis of the muscular septum in the region of the bundle of His consequent on a recent thrombosis of its nutrient arteries."

Neuhof²⁴ described a case of complete heart-block and auricular fibrillation in a woman of eighty-three years who died in heart failure. At autopsy the coronary artery was found thickened and sclerosed although slightly patulous (he does not state which coronary) and the artery supplying the A-V node was completely calcified.

Carter and McEachern²⁵ reported a case of recurrent complete heart-block in an individual with general and coronary arteriosclerosis. They too regarded the sudden and frequent shifting from normal sinus rhythm to complete heart-block as being dependent upon vascular sclerosis with a deficient blood supply to the A-V node.

Levine's case (Case 14, Table I) was the only instance in which the left coronary artery alone was involved, or rather where the right coronary artery was not at all involved, and probably falls into the 8 per cent group in which the artery to the A-V node arises from the left coronary artery after crossing the "crux" of the heart.

CLINICAL SIGNIFICANCE

The clinical differentiation between right and left coronary artery occlusion has engaged the attention of many clinicians. The work of numerous investigators,^{7, 8, 9, 16} shows that infarction of that portion of the myocardium usually supplied by the right coronary artery is associated with inversion of the T-waves in Leads II and III, whereas infarction of the myocardium supplied by the left coronary artery is associated with inversion of the T-waves in Leads I and II. The appearance of complete heart-block during an attack of acute coronary artery thrombosis points to involvement of the right coronary artery in about 93 per cent of the cases. If in addition to this we have other clinical signs such as rapid enlargement of the liver, as emphasized by Libman, the clinical diagnosis of right coronary artery occlusion can be made with greater certainty.

SUMMARY AND CONCLUSIONS

A case of transient complete heart-block occurring during an attack of acute coronary artery thrombosis is described in detail. Changes in the ventricular portion of serial electrocardiograms conform to type T₃, indicating myocardial damage as the result of occlusion of the right coronary artery.

The transient nature of A-V dissociation during an attack of coronary artery thrombosis has been explained on the basis of the peculiar anat-

omy of the blood supply to the A-V node. Permanent heart-block without any demonstrable lesions of the node or main stem may be explained on the same basis.

The observations on the case presented and a review of similar cases reported in the literature indicate that in patients with coronary artery occlusion and complete heart-block, the right coronary artery is involved in approximately 93 per cent of the cases and the left in 7 per cent. The presence of complete A-V dissociation is therefore believed to be a valuable diagnostic criterion in the clinical differentiation between right and left coronary artery thrombosis.

I am greatly indebted to Dr. Marcus A. Rothschild, Dr. Sidney P. Schwartz, and Dr. Ernst P. Boas for furnishing me with clinical data and electrocardiograms of cases which they observed but have not published.

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THE EFFECT OF TONSILLECTOMY ON THE OCCURRENCE AND COURSE OF ACUTE POLYARTHRITIS*†

AN ANALYSIS OF 654 CONSECUTIVE CASE HISTORIES

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THE problem of focal infection and its relation to the etiology of rheumatic diseases and their recurrence has been much studied and discussed in recent years. Recent work upon the bacteriological and immunological aspects of rheumatic diseases has emphasized the importance of this concept, and most writers have stressed the rôle of the tonsils as an important focus. The object of this paper is to consider the present day beliefs concerning this possible source of systemic infection.

Tonsillitis, acute or chronic, is a medical disease and as such is usually entirely under the direction of the general practitioner. Even in the eventuality of tonsillectomy the patient is urged or dissuaded according to the beliefs or doubts of his medical adviser.

The virulence of a given attack of tonsillitis is difficult to estimate. A seemingly mild tonsillitis may have dire effects upon other structures, while a much more violent local reaction may pass, leaving little but weakness and prostration, and be followed by apparently complete recovery. The physician has little difficulty in recognizing an attack of acute tonsillitis. The diagnosis of the chronic form may be more difficult. Slight degrees of sore throat may make but little impression on the patient's mind, and he may fail to mention them in giving his medical history, or they may not have recurred for so many years that they are entirely forgotten. In attempting to explain undefined ill health, the physician should take into consideration a history of previous sore throats, for the tonsils once infected, even though quiescent for years, have proved in numerous cases still to harbor infection.

It has been shown¹ that the tonsils may be enucleated with safety during the acute stage of rheumatic fever. The present study was made to determine, if possible, whether or not the enucleation of the tonsils at any time has any effect upon the recurrence of rheumatic fever. Since our material is based entirely upon the examination of case histories, no

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great emphasis can be laid upon the accuracy of details. The results, however, have brought out interesting comparisons and observations.

For the purposes of this study consecutive cases were taken from the four medical services of the Boston City Hospital during a five-year period between January 1, 1924, and December 31, 1928. Such a period was chosen to avoid, if possible, annual fluctuations in the occurrence of rheumatic diseases and in the type of manifestations. In order to limit the size of the study and to secure an easily segregated and clean-cut group of cases, only those admitted for acute migratory polyarthritis were selected. Any who were suspected of having specific etiology or who later developed permanent changes in the joints were excluded. Of a total of 654 cases thus obtained, 114 had been operated upon for tonsillectomy prior to admission. Our attention was directed chiefly to tonsillectomy and its results, since the medical treatment was essentially the same in all. The latter consisted primarily of large doses of salicylates or their substitutes when the former were not well tolerated. In addition to determining the efficacy of tonsillectomy in the various aspects of the disease, other interesting observations were thought worthy of recording as they have brought out points not commonly appreciated.

ANALYSIS OF CASE HISTORIES

Age and Sex Distribution.—The distribution of the cases according to decades and between the sexes is shown in Table I, and the percentage in-

TABLE I
AGE AND SEX INCIDENCE

AGE (YEARS)	MALES	FEMALES	MALES AND FEMALES	PERCENTAGE OF TOTAL
12-19	90	65	155	23.7
20-29	97	90	187	28.6
30-39	87	54	141	21.5
40-49	61	43	104	15.9
50 and over	44	23	67	10.2
	<hr/> 379	<hr/> 275	<hr/> 654	<hr/> 100.

idence of cases in the various decades, when allowance is made for the fact that no patients are admitted to the regular medical wards before the age of twelve years, shows a progressive decline with increasing age. There is also a predominance of males, approximately in the proportion of three to two. The predominance of males may be in part accounted for by the character of the hospital population. This, however, was not analyzed in detail. It is interesting to observe the large number of persons in the older age groups, a fact not commonly appreciated. The figures in some of the later tables are also arranged according to decades

in order to emphasize the similarity of the various details of the disease in the later as well as in the earlier decades.

Incidence of Recurrences.—In the group of 654 cases studied, 335 were admitted for an initial attack, and the remaining 319 cases, or 49 per cent, were admitted for recurrences. The percentage of cases in each age group with previous attacks of polyarthritis is strikingly uniform (Table II).

TABLE II
FREQUENCY OF PREVIOUS ATTACKS OF ACUTE POLYARTHRITIS

AGE GROUP	CASES IN AGE GROUP	CASES WITH PREVIOUS POLYARTHRITIS	PERCENTAGE OF AGE GROUP
12-19	155	72	46.5
20-29	187	89	47.6
30-39	141	65	46.1
40-49	104	50	48.1
50 and over	67	43	64.2
All ages	654	319	48.8

Recurrences in Relation to Previous Tonsillectomies.—In Table III are shown the numbers and percentages of patients in each of the various decades who were admitted for initial or subsequent attacks of acute migratory polyarthritis, and who had been previously subjected to tonsillectomy. It is seen that 42, or 6.4 per cent, of the patients who were admitted for an initial attack had already had their tonsils removed. Seventy-two cases, or 11 per cent, were admitted for subsequent attacks after tonsillectomy, giving a total of 114 cases or 17.4 per cent of a total of 654 cases admitted for acute polyarthritis subsequent to tonsillectomy. In other words, of the 335 patients admitted for an initial attack 42, or 13 per cent, had previously had tonsillectomy, whereas 72, or 23 per cent,

TABLE III
FREQUENCY OF HISTORY OF RECURRENT ATTACKS OF POLYARTHRITIS IN CASES PREVIOUSLY SUBJECTED TO TONSILLECTOMY

AGE GROUP (YEARS)	CASES IN AGE GROUP	CASES WITH PREVIOUS TONSILLECTOMY					
		TOTAL CASES	PERCENT-AGE OF AGE GROUP	ADMITTED FOR INITIAL ATTACK	PERCENT-AGE OF AGE GROUP	ADMITTED FOR RECURRENCE	PERCENT-AGE OF AGE GROUP
12-19	155	58	37.4	25	16.1	33	21.3
20-29	187	34	18.2	12	6.4	22	11.8
30-39	141	18	12.7	5	3.5	13	9.2
40-49	104	4	3.8	0	0	4	3.8
50 and over	67	0	0	0	0	0	0
All ages	654	114	17.4	42	6.4	72	11.0

of the 139 patients admitted for recurrences previously had had tonsillectomy. Thus twice the percentage of cases previously subjected to operation were admitted for a recurrence as were admitted for an initial attack. The proportion is quite similar in each of the age groups.

Frequency of Sore Throat in Relation to Tonsillectomy.—In this category are included all cases who had had sore throats, diagnosed "septic throat," "acute tonsillitis," "acute pharyngitis" or similar diagnoses, in which the throat symptoms began either with the onset of the joint symptoms or preceding them by a period not exceeding fourteen days. There were in all 281 cases, or 43 per cent, having sore throats with or before the attack. Of the 114 cases who had previously had a tonsillectomy 50, or 44 per cent, began with sore throats, whereas 231, or 43 per cent, of the 540 cases not previously subjected to the operation had had an antecedent sore throat. It would appear that the attack of acute polyarthrititis was just as frequently preceded by throat symptoms in the group subjected to tonsillectomy sometime previous to admission as in those who had never been operated upon. In this same connection, it is interesting to note that 50, or 44 per cent, of the 114 cases who had had their tonsils removed before entry, were found to have tonsillar tissue on simple inspection of the throat during the admission physical examination.

Frequency of Rheumatic Heart Disease.—The frequency with which a diagnosis of rheumatic heart disease was made or suspected at the time of entry in the present group of cases is shown in Table IV. It is seen that 67, or 59 per cent, of the 114 cases previously operated upon had, or were suspected of having, heart involvement at the time of entry. Among the cases who had no previous operation, 202, or 37 per cent, had, or were suspected of having, rheumatic heart disease on admission to the hospital. This makes a total of 269, or 41 per cent, of all of the cases with heart lesions diagnosed or suspected at entry. Among these cases

TABLE IV

FREQUENCY WITH WHICH THE DIAGNOSIS OF "RHEUMATIC HEART DISEASE" WAS MADE OR SUSPECTED AT THE TIME OF ADMISSION

AGE (YEARS)	CASES WITHOUT PREVIOUS TONSILLECTOMY			CASES WITH PREVIOUS TONSILLECTOMY			ALL CASES		
	CASES IN AGE GROUP	R. H. D. DIAG- NOSED	R. H. D. SUS- PECTED	CASES IN AGE GROUP	R. H. D. DIAG- NOSED	R. H. D. SUS- PECTED	CASES IN AGE GROUP	R. H. D. DI- AGNOSED AND SUS- PECTED	PERCENT- AGE OF AGE GROUP
12-19	97	28	26	58	25	11	155	90	58.1
20-29	153	32	25	34	15	7	187	79	42.2
30-39	123	15	16	18	4	4	141	39	27.7
40-49	100	21	10	4	1	0	104	32	30.8
50 and over	67	15	14	0	0	0	67	29	43.3
All ages	540	111	91	114	45	22	654	269	41.1

heart lesions were therefore about one and one-half times as frequent in those whose tonsils had been removed as they were in those not subjected to the operation.

When analyzed according to whether the patients were admitted for the first or for a subsequent attack, it was seen that 92, or 29 per cent, of the 319 cases admitted for the first attack had had, or were suspected of having, heart involvement at the time of entry, as compared to 175, or 53 per cent, of the 335 patients admitted for a recurrent attack who were similarly affected. In other words, rheumatic heart disease was about twice as frequent in the group of cases admitted for recurrent attacks as among those admitted for an initial attack. Considering both of these findings it may be said that previous tonsillectomy had no striking effect in reducing the incidence of cardiac lesions at the time of admission to the hospital in this series of cases.

EFFECT OF TONSILLECTOMY ON THE ATTACK

For the purpose of comparing the cases which had never been subjected to tonsillectomy with those admitted subsequent to the operation and also with those subjected to tonsillectomy during their stay in the hospital, it was necessary to choose certain criteria which were both simple and easy to determine from the case records. Three such facts were selected:

1. The duration of joint symptoms.
2. The duration of fever.
3. The duration of hospitalization.

Fever was considered present when the temperature rose to or above 99.4° F. In order to ascertain whether or not the cases were comparable at the time of admission to the hospital, the only criterion that could be used was the first, namely, the duration of joint symptoms at the time of admission, this being the most reliable symptom obtainable from the patient.

Duration of Joint Symptoms at Entry.—In Table V is shown the duration at the time of entry of the joint symptoms in the cases studied. These were subdivided into groups according to the duration of symptoms and the patients divided further into those previously operated upon, those operated upon in the hospital, and those having no operation. The percentage incidence in each of the latter groups is indicated in the table and is shown graphically in Fig. 1. From this illustration it may be seen that the groups were quite comparable with regard to the duration of joint symptoms at the time of entry, the curves for each of these groups running closely together and crossing frequently.

Total Duration of Joint Symptoms.—The cases were analyzed in a similar manner with regard to the total duration of symptoms from the time of onset to the time when the joint symptoms were last noted, and the results are shown in Table VI and represented graphically in Fig. 2.

TABLE V
DURATION OF JOINT SYMPTOMS AT ENTRY*

DURATION AT ENTRY (DAYS)	OPERATION BEFORE ADMISSION		OPERATION DURING HOSPITALIZATION		NO OPERATION	
	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION
0-7	51	44.7	52	34.2	151	38.4
8-15	20	17.5	30	19.7	94	23.9
16-31	27	23.8	42	27.6	99	25.2
32-63	10	8.8	20	13.2	40	10.2
64+	6	5.3	8	5.3	9	2.3
All cases	114	100.0	152	100.0	393	100.0

*Including cases reoperated during hospitalization.

Cases where data were not given are excluded in this and the following tables.

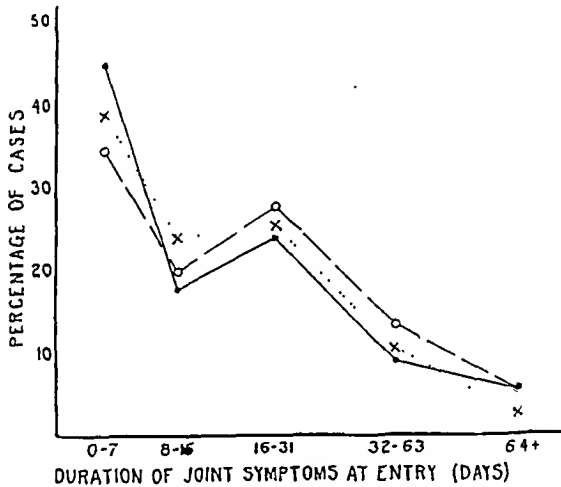


Fig. 1.—In this and the following illustrations:
 — Cases with tonsillectomy before admission.
 o- - - - - Cases having tonsillectomy in hospital.
 x. Cases without tonsillectomy.

From a study of the latter figure, it appears that the cases previously subjected to tonsillectomy, as indicated by the solid line connecting the dots, and the cases having no operation, as represented by the dotted line connecting the crosses, were quite comparable with respect to the total duration of the joint symptoms, inasmuch as these curves are not widely divergent and cross early and again later. On the other hand, the cases that were operated upon in the hospital, indicated by the interrupted line connecting the circles, have a lower incidence among the groups having a short duration and a slightly higher incidence among those having a longer duration of joint symptoms. This does not appear very strikingly but is definitely suggestive. It is, however, quite comprehensible if we consider that a number of patients who were operated upon during a pe-

TABLE VI
TOTAL DURATION OF JOINT SYMPTOMS

DURATION (DAYS)	OPERATION BEFORE ADMISSION		OPERATION DURING HOSPITALIZATION		NO OPERATION	
	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION
15 or less	33	29.2	26	17.0	95	25.3
16-30	29	25.7	45	29.4	122	32.5
31-60	33	29.2	52	34.0	122	32.5
61-90	8	7.1	19	12.4	25	6.7
91 or more	10	8.9	11	7.2	11	2.9
	113	100.0	153	100.0	375	100.0

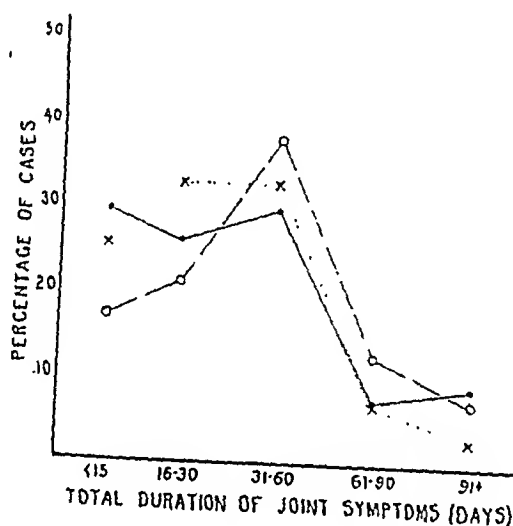


Fig. 2.

riod when they were not having joint symptoms had a recrudescence of symptoms subsequent to the operation.

Duration of Fever in the Hospital.—The cases were studied with respect to the total number of days of elevated temperature above 99.4° F., and the results tabulated in a manner similar to that in which the joint symptoms were studied. The results are shown in Table VII and represented graphically in Fig. 3. The three curves in this figure are of the same form and run very close together, showing that with respect to the duration of fever in the hospital there was very little difference between those patients having had no tonsillectomy at all, those subjected to this operation before entry, and those operated upon in the hospital.

Duration of Hospitalization.—A similar study was made of the duration of hospitalization in these cases, and the results are shown in Table VIII and in Fig. 4. Here we see a progressive change in the shape of the curves, the curve representing the cases which had had no tonsil-

TABLE VII
DURATION OF FEVER IN THE HOSPITAL

DURATION (DAYS)	OPERATION BEFORE ADMISSION		OPERATION DURING HOSPITALIZATION		NO OPERATION	
	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION
0-7	80	70.1	107	68.1	289	72.8
8-15	15	13.2	30	19.1	54	13.6
16-30	13	11.4	14	8.9	40	10.1
31+	6	5.3	6	3.8	14	3.5
	114	100.0	157	100.0	397	100.0

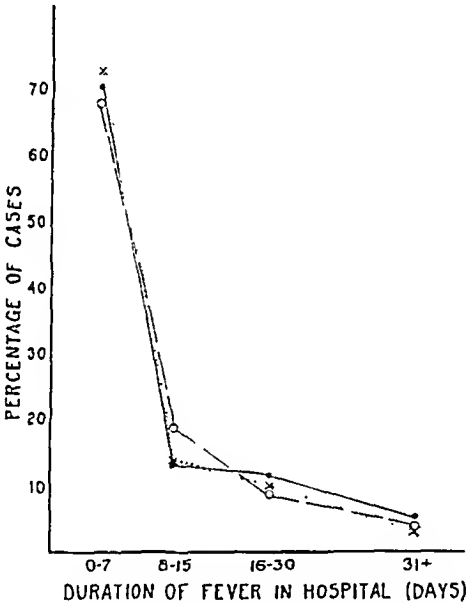


Fig. 3.

lectomy at all having the smallest percentage of cases in the shorter periods, and the greater percentage of cases in the longer periods. The cases subjected to tonsillectomy during the stay in the hospital have the lowest percentage in the shorter periods of hospitalization and the highest in the longer periods. The patients subjected to tonsillectomy before entry to the hospital, occupy an intermediate position. In other words, the patients who had no tonsillectomy at all had on the whole the shortest stay in the hospital, and those subject to tonsillectomy before entry had a somewhat longer period but were not in the hospital as long as those patients who were operated upon during their stay. The difference between those operated on before entry and those not operated on at all is only slight, but those operated on in the hospital show a fairly wide divergence.

TABLE VIII
DURATION OF HOSPITALIZATION

DURATION (DAYS)	OPERATION BEFORE ADMISSION		OPERATION DURING HOSPITALIZATION		NO OPERATION	
	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION	NUMBER OF CASES	PERCENTAGE DISTRIBUTION
15 or less	31	27.2	19	12.1	139	35.0
16-30	34	29.8	51	32.5	124	31.1
31-60	36	31.6	67	42.7	103	26.2
61+	13	11.4	20	12.7	31	7.8
	<u>114</u>	<u>100.0</u>	<u>157</u>	<u>100.0</u>	<u>397</u>	<u>100.0</u>

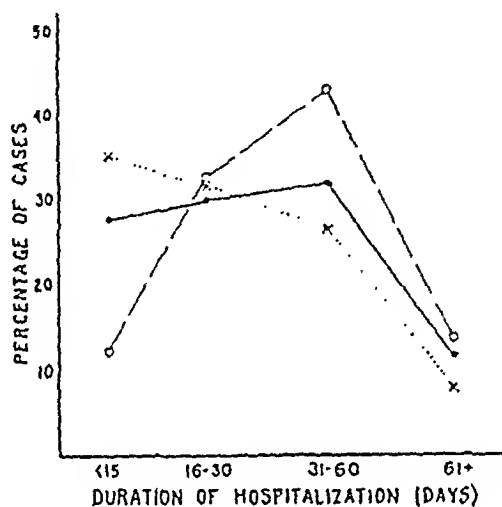


Fig. 4.

Evidence of Active Rheumatic Heart Disease During Observation.—Patients were considered to have active rheumatic heart disease when one of the following was present: changing endocardial murmurs, pericarditis, pancarditis, arrhythmias, disturbances of conduction, easily accelerated pulse rate, or decompensation.

Among the 114 patients who had had a tonsillectomy before entry, 33, or 29 per cent, had active rheumatic heart disease while under observation, as compared to 104, or 19 per cent, of those patients who had had no tonsillectomy before entry. When the latter cases are subdivided into those operated upon in the hospital and those having no operation at all, we find that 21, or 15 per cent, of the 143 patients operated upon in the hospital who were not previously subjected to tonsillectomy, were observed to have active rheumatic cardiac lesions, whereas 83, or 21 per cent, of the 397 cases who were at no time subjected to tonsillectomy had similar lesions. It is only fair to assume that the lowest figure of 15 per cent among those patients operated upon in the hospital depends largely

upon the choice of cases for operation, inasmuch as most of the physicians in the hospital have advised against operating upon patients in whom active lesions were observed. However, the high incidence of active rheumatic heart lesions in the group admitted to the hospital subsequent to tonsillectomy is striking. It must, of course, be considered that these cases may represent the poorer risks, inasmuch as patients having frequent attacks as shown above are more subject to rheumatic heart disease, and they are the ones usually recommended by physicians for tonsillectomy. When analyzed on the basis of the diagnosis of rheumatic

TABLE IX
POSTOPERATIVE COMPLICATIONS (CASES OPERATED ON WHILE SYMPTOMS OF THE ACUTE DISEASE WERE STILL PRESENT ARE EXCLUDED)

MANIFESTATIONS	NUMBER OF CASES
Leucocytosis, with or without fever	18
Fever, leucocytosis and active cardiac lesion	6
Fever and arthritis	21
Arthritis or nodules or both	4
Severe sore throat with fever	2
Peritonsillar abscess	1
Postoperative hemorrhage	3

heart disease at entry, it was seen that 93, or 34 per cent, of 269 patients having rheumatic heart disease at the time of entry showed active cardiac lesions during their stay, whereas 44, or 11 per cent, of those patients not diagnosed or suspected of having rheumatic heart disease at entry had active rheumatic cardiac lesions during their stay in the hospital. That is to say, according to the criterion mentioned, about one-third of the patients who were admitted with some rheumatic cardiac lesion were active during the attack for which they were admitted, whereas 11 per cent of those not suspected of having any cardiac lesion at the time of entry developed evidence of lesions. Minor differences were observed between those patients operated on before entry and those not operated on.

Postoperative Complications.—In Table IX are listed the number of cases in which various complications occurred among those operated upon in the hospital, excluding the patients whose operation was performed during the acute stage of the disease. Approximately one-half of the patients who were operated upon while apparently quiescent showed evidence of activity following the operation, but in only six were there serious complications, as evidenced by the presence of active heart lesions following operation.

INCIDENCE OF INITIAL ATTACKS AND RECURRENCES IN RELATION TO
TONSILLECTOMY

Age at First Attack.—In Table X the cases are grouped according to the decade at which the first attack occurred. It is, of course, seen that except for the earliest age group, the incidence of initial attacks declines progressively with each decade. The 41 patients admitted for a first attack subsequent to the removal of their tonsils are also grouped by decades. The absence of patients beyond the age of forty years possibly depends upon the rarity with which older individuals are recommended

TABLE X
AGE AT TIME OF FIRST ATTACK OF POLYARTHRITIS*

AGE AT TIME OF FIRST ATTACK	ALL CASES*	CASES NOW ADMITTED FOR FIRST ATTACK	
		WITH PREVIOUS TONSILLECTOMY	WITHOUT PREVIOUS TONSILLECTOMY
0-9	40		
10-19	210	25	56
20-29	164	12	82
30-39	117	4	67
40-49	72	0	53
50 and over	33	0	21
Total	636	41	279

*Excluding 18 cases with incomplete data. In the subsequent tables the cases with insufficient data are excluded.

for this operation rather than upon the frequency with which attacks tend to recur. The last column, indicating the patients who were admitted for an initial attack, again emphasizes the fact that although there is a progressive decline in incidence with each advancing decade, there is still a large number whose first observed attack occurs after the fourth decade.

Frequency of Attacks.—An attempt was made on the basis of the data obtained from the records to determine the frequency with which attacks occur according to the age at the onset of the disease, and also to determine the number of attacks in each of these age groups. The data for the cases not previously subjected to tonsillectomy are shown in Table XI. In general no marked differences are observed in the frequency with which attacks recur in the various age groups, although there appears to be some tendency for attacks to be farther apart through the fourth decade, and then to be more frequent again in the later decades. The average number of recurrences is only very slightly lower in those having their initial attack in the later decades. In Table XII the results of a similar study in those cases previously subjected to tonsillectomy are given. Here it will be seen that the average number of recurrences in

those cases admitted following tonsillectomy is about the same as those not previously operated upon. The attacks, however, are much closer together in the cases previously tonsillectomized. The attacks occurred on an average at the rate of one recurrence every 3.2 years in this group as compared to one every 5.4 years in those not previously operated upon. It is interesting to observe that in the patients previously operated upon the average lapse from the time of tonsillectomy to the time of entry was

TABLE XI

FREQUENCY OF ATTACKS IN CASES NOT PREVIOUSLY SUBJECTED TO TONSILLECTOMY

AGE AT INITIAL ATTACK	CASES ADMITTED FOR RECURRENCE	FREQUENCY OF RECURRENCE*	AVERAGE NUMBER OF ATTACKS
0-9	23	4.7	4.0
10-19	90	5.6	3.1
20-29	58	5.7	2.8
30-39	41	6.8	2.5
40-49	18	4.5	2.9
50 and over	12	3.1	3.3
All cases	242	5.4	3.0

*Average lapse, in years, between attacks.

TABLE XII

FREQUENCY OF ATTACKS IN CASES PREVIOUSLY SUBJECTED TO TONSILLECTOMY

AGE AT INITIAL ATTACK	CASES ADMITTED FOR RECURRENCE	FREQUENCY OF RECURRENCE	AVERAGE NUMBER OF ATTACKS	FREQUENCY OF RECURRENCE AFTER TONSILLECTOMY	AVERAGE NUMBER OF ATTACKS AFTER TONSILLECTOMY
0-9	16	4.2	3.4	3.8	2.1
10-19	37	2.9	3.1	2.9	2.1
20-29	11	4.7	2.5	3.9	1.8
30-39	5	2.1	2.4	2.4	1.2
40-49	1	0.7	4.0	0.5	4.0
50 and over	0	0.	0.	0.	0.
All cases	70	3.2	3.1	3.2	2.0

6.5 years and during this period there occurred an average of 2.0 attacks per patient. The frequency of attacks following tonsillectomy is strikingly similar in these cases to the frequency of recurrences following the initial attack. Sixty-five of the patients who were subjected to tonsillectomy before admission to the hospital were this time admitted for the first attack after their operation. Forty of these patients had had no attacks previously and twenty-five had attacks before their operation. The average lapse of time from the operation to the time of entry in those who had never had previous attacks was 6.4 years, and in the twenty-five patients now admitted for a recurrence—this being the first attack after

the operation—the lapse from the time of tonsillectomy averaged 6.0 years. The figures are strikingly similar.

COMMENT

The cases included in the analysis here presented were very carefully chosen in such a manner that no doubt can exist as to the type of cases admitted. No claim is made that all of these cases represent cases of rheumatic fever, and no attempt is made into the controversy as to the differentiation of those cases of acute polyarthritis which may be included under the term rheumatic fever and those which should be designated acute infectious arthritis. Whether or not these cases should be so differentiated is of no great significance from the point of view of the material at hand. In this present study, and from the material analyzed, such differentiation was well-nigh impossible.

The operation of tonsillectomy has been recommended and is being recommended for patients with rheumatic diseases by a large majority of physicians in face of a great amount of accumulated evidence tending to indicate that this operation has had very little or no demonstrable benefit upon the possibility of recurrences. The present data only confirm the previous work on this subject. It is further shown here that the individual attack is practically unaffected by the fact of previous removal of tonsils. The findings of more frequent attacks in patients previously subjected to tonsillectomy may, of course, have its basis in the fact that patients are recommended for tonsillectomy only when they are observed to have frequent attacks, and the longer duration of joint symptoms, as well as the long duration of hospitalization, as has already been inferred, is probably due to the number of patients having slight recurrences following the operation who are kept in the hospital a somewhat longer period in order to be observed following their operation.

On the basis of the frequent observation of sore throats preceding rheumatic manifestations, as intimated in the findings recorded, it would seem that removal of tonsils should eradicate an important focus of infection and thus decrease the possibilities of recurrences. In individual cases, apparently striking benefit is observed even when the tonsils are enucleated during the disease, but obviously this is not always the case. The explanation for the poor results following operation is not entirely clear. We have mentioned above that about one-half of the operated cases were recorded as having tonsillar tissue at the time of admission. It is possible that incomplete removal of tonsils may be harmful, as the infected focus may become buried in scar tissue following the operation. Other foci may be overlooked or inaccessible.

Finally, what deductions shall we make from this investigation? In a large series of cases such as have been reported here and in other studies it must be remembered that a great number of operators of varying degrees of experience is represented. It is a question whether such large

groups of cases gathered in this manner from the records of a large municipal hospital give a true estimate of tonsillectomy as a preventive of rheumatic fever. In private practice where the cases can be studied with great care and an operator of experience in this particular operation can be selected, the results are often far more satisfactory. One of us (W. H. R.) after years of private practice, feels that when this has been done, the procedure has often been highly justifiable and has fully accomplished its aim.

SUMMARY

The case records of 654 consecutive patients admitted to the Boston City Hospital for acute migratory polyarthritis were studied for the purpose of determining whether or not tonsillectomy has altered the course of the attack or has affected the frequency of recurrence.

Patients admitted to the hospital for acute polyarthritis who had been operated upon sometime previously had on the whole a very similar course in the hospital, as judged by the duration of joint symptoms, the duration of fever, and the duration of hospitalization, as those operated upon after admission to the hospital.

Patients subjected to tonsillectomy during their stay in the hospital for acute migratory polyarthritis had a slightly longer period of joint symptoms and of hospitalization than those not operated upon during their stay.

Tonsillectomy has had very little influence in these cases upon the frequency of recurrent attacks.

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ARRHYTHMIA OF THE HEART ASSOCIATED WITH CHEYNE-STOKES BREATHING*

REPORT OF A CASE SHOWING AURICULOVENTRICULAR BLOCK

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THE number of reports that have been published of cases in which fundamental disturbances of the rhythm of the heart were found associated with Cheyne-Stokes respiration are few, although difference in cardiac rate between the apneic and respiratory phases has been common knowledge for many years. In the literature descriptions of only twelve cases of cardiac arrhythmia with extreme slowing of the rate during the respiratory phase other than simple changes of rate associated with the phases of Cheyne-Stokes respiration have been found, four of which have been studied by means of the electrocardiograph. The following case may, therefore, be not without interest.

M. S., Hospital No. 7507, a colored woman, fifty years of age, was admitted to hospital, September 24, 1930, complaining of shortness of breath and swelling of the legs. The past history was unimportant. No serious illnesses had been experienced before 1928, when slight rheumatic pains in both shoulders occurred, and the whole body, including the face and tongue, are said to have become swollen. At this time her blood pressure was found to be 200 mm. Hg systolic and continued at this level until two weeks before admission.

The onset of sudden attacks of intense dyspnea "like asthma" occurring almost every morning while walking to work culminated in a very severe attack with palpitation on July 4, 1929, relieved only by a hypodermic injection of unknown content. She stopped work, remaining at home until the second week of September, 1929, when the attacks of dyspnea disappeared but palpitation continued to recur on exertion. Work was now resumed for nine months during which she remained fairly well until edema of the ankles first appeared in July, 1930. Two days later, after climbing five flights of stairs, a severe attack of dyspnea occurred, the first one since September, 1929. From this time until admission her condition grew steadily worse; shortness of breath increased and edema extended from the legs to the thighs. By the end of August it involved the lower abdominal wall. Pain in the right upper quadrant of the abdomen appeared at this time and increased steadily in severity.

On admission, the patient was seen to be a moderately well developed and well nourished colored woman suffering from severe orthopnea and periodic dyspnea of Cheyne-Stokes type. There was frequent dry cough. No unusual conditions except those pertaining to cardiovascular disease were found during examination. The bases of the lungs on both sides were at the level of the tenth spinous process. The descent of the left lung on inspiration was less than that of the right. There were no areas of dullness. Many râles were present in the lower portions of both lungs.

The apical impulse of the heart was diffuse, but forceful. No thrills or shocks

*From the Hospital of the Rockefeller Institute for Medical Research, New York.

were felt. The maximal width of the area of relative cardiac dullness was in the fifth interspace, extending 14 cm. to the left of the midline, and 4.5 cm. to the right. A loud systolic murmur was present over the chest, front and back, louder on the left side. The second aortic sound was faint. An x-ray photograph taken on September 25 showed well marked enlargement of the heart to both the left and right sides, and dilatation of the aortic arch. The lung fields were hazy and the shadows at the hila were consistent with chronic passive congestion. The heart exhibited sinus rhythm with slowing of the rate during dyspnea. The systolic blood pressure measured 160, the diastolic 95 mm. of mercury. The pulse was of variable volume, becoming somewhat weaker and slower during the respiratory phases. The abdomen was protuberant and tympanitic. The liver was tender and extended 3 cm. below the costal margin. The spleen was not palpable. There was dullness in the lower part of the abdomen suggesting the presence of a small amount of fluid. Anasarca of the lower part of the back and of the legs was present. Pitting on pressure was easily demonstrated.

The urine did not reduce Benedict's solution. Albumin was present in large amounts. There were many hyalin and granular casts, red blood cells, white blood cells and epithelial cells. The standard urea clearance test was 37 per cent of normal (September 29). On September 25, the count of the red blood cells was 4,500,000. Estimation of hemoglobin (Sahli) was 88 per cent. The total white blood cells numbered 13,000, of which polymorphonuclear leucocytes were 77 per cent, lymphocytes 18 per cent, and mononuclears 5 per cent. The Wassermann reaction of blood serum was negative (September 26).

During the first forty-eight hours in hospital, edema increased and the Cheyne-Stokes cycles became longer, so that digitalis (digitan, Merck) 1.0 gm. was given on September 26, without waiting for the usual period of observation to elapse. Only a slight increase in urinary output followed and gain in weight continued. The administration of theocalcin was also of no avail. On September 30, a change in cardiac mechanism was noted—the transition from a slow rate during the respiratory phase to a rapid one during the apneic, became abrupt; the rate during apnea reached 160 per minute. When, on October 9, extreme slowing appeared during dyspnea, there having been no sign of improvement, digitan, which had been administered at the rate of 0.1 gm. a day, was discontinued.

The general condition of the patient then grew progressively worse; unconsciousness supervened during apneic phases which had now increased to thirty-five seconds in length. In contrast to these unfavorable circumstances, the grave disturbances of cardiac rhythm which had been present were replaced by the gradual moderate slowing such as had been observed during the respiratory phase on admission. Steady accumulation of edema was retarded for a brief period by the administration of salyrgan on October 24 and 26. Subsequent exhibition of 1.8 gm. of digitan between November 10 and 15 failed to be of any benefit. Use of the drug was stopped on the latter date because of the development of periods of coupled rhythm which bore little relation to the rhythm of the Cheyne-Stokes cycles. The inhalation of increased concentrations of oxygen failed to stop the periodicity of respiration, but increased concentrations of carbon dioxide always succeeded in doing so. Neither gas had any consistent effect upon the cardiac rhythm. On November 19 the patient became deeply comatose, the breathing continuously dyspneic, and the rhythm of the heart regular, continuing so until death on November 20.

On postmortem examination* the body was seen to be that of a well developed and well nourished adult negress. Soft edema of the feet, ankles and legs was present. The surfaces of the pleurae were smooth and glistening, except for occasional fine fibrous adhesions, especially at the apices. About 100 c.c. of thin, straw-colored fluid

*We are indebted to Dr. C. P. Rhoads for the report of this examination.

was present in the left, and about 200 c.c. in the right thoracic cavity. The surfaces of the lungs were smooth except for a few adhesions and several rounded, slightly raised areas 2 to 3 mm. in diameter, firm in consistency, yellowish gray on section, surrounded by a firm, fibrous capsule. The surface of the lungs was purple and glistening, and distended alveoli were clearly visible. The cut surface and the bronchi exuded thin, blood-tinged fluid. The pulmonary artery showed a moderate degree of atheromatous change in the prepulmonary part.

The pericardial cavity contained about 60 c.c. of thin, yellow fluid. The surfaces were smooth and glistening. The heart weighed 640 grams. As viewed in situ before section of the great vessels, the greatest diameter was 18 cm. from the apex to the midportion of the right auricle. The superior inferior diameter of the right auricle was 10.5 cm. There was very marked increase in the size of the heart, particularly of the right side. The epicardium was smooth and glistening and revealed a patch of fibrosis, gray in color, on the anterior surface of the left ventricle which measured about 3 cm. in diameter. The myocardium was firm, dark purplish red in color, and presented no gross evidence of sclerosis. The endocardium and the valves were without change. The coronary arteries showed a moderate number of raised, irregular, atheromatous plaques. The tricuspid valve measured 12.5 cm. in circumference, the pulmonary valve 9.0 cm., the mitral valve 12.0 cm., the aortic valve 8.7 cm. The thickness of the wall of the left ventricle was 1.6 cm., and that of the right 0.4 to 0.6 cm.

The aorta displayed a number of raised, irregular, yellow to yellow-white plaques, particularly marked in the arch and descending aorta. Ulceration, though rare, was occasionally seen. Otherwise the vessels of the thoracic and abdominal cavities did not present abnormalities.

The spleen and liver were both moderately and symmetrically enlarged showing the usual changes attributed to chronic passive congestion. A well marked infiltration of fat was present in the liver.

The right kidney was normal in appearance. The left, however, was markedly atrophied, weighing only 44 grams. The surface was nodular and two small cysts containing a cloudy fluid were present. The cortex was extremely irregular in thickness and in structure. The glomeruli, however, could be easily seen.

The combined weight of the adrenal glands was 60 grams. They were normal in size, color, shape and consistency. The pancreas weighed 80 grams and was likewise normal. No other unusual findings were observed. Permission for the removal of the brain was not granted.

On microscopic examination the heart and the bundle of His were without abnormality. The aorta showed a moderate degree of intimal thickening of a type attributable to arteriosclerosis.

The pulmonary alveoli contained a large amount of precipitated albumin. The capillaries of the alveolar wall were enormously distended, and the walls themselves seemed much thicker than is common, apparently due to increase in cells of interstitial tissue, nonneutrophils or fibroblasts. Many heart failure cells were present.

The liver, kidneys and spleen all presented marked intimal thickening of the smaller vessels and extreme passive congestion. The strands of liver cells became more and more shrunken and vacuolated as the center of the lobule was approached, until they were entirely replaced by erythrocytes. In addition to the changes in the kidney already mentioned, many sclerosed and hyaline glomeruli, and many dilated and atrophied tubules were seen. The adrenal glands were normal.

The anatomical diagnosis was hypertrophy and dilatation of the heart; congestion of lungs, liver, spleen and kidneys; arteriosclerosis of aorta and coronary vessels; healed tuberculosis of lung and spleen; ascites and hydrothorax. The microscopic diagnosis was congestion of lung, spleen and liver; generalized arteriosclerosis.

ELECTROCARDIOGRAMS

A study of the first electrocardiogram which was obtained on September 25, shows slowing of the cardiac rate during the respiratory phase which was noted also on direct physical examination (Fig. 1). The average rate during the respiratory phase is 83, but it varies from 72 to 108 per minute. During the respiratory phase, P_1 changes in form, being frequently inverted. Since the variant P-waves occur when the interauricular intervals are longest, it seems probable that marked slowing of the normal pacemaker allows a lower portion of the auricle or a portion of the auriculoventricular system to take over this function. P_2 during an apneic phase becomes regular at a rate of 115 per minute and is constant in form with the exception of the last complex but one.

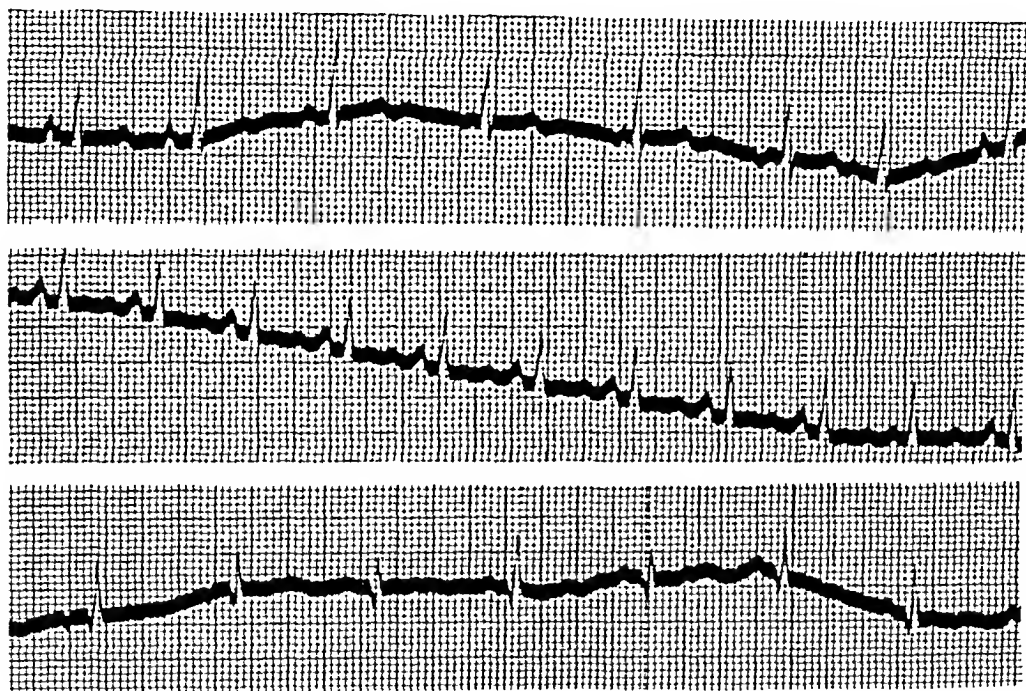


Fig. 1.—The three standard leads in order from above downward are shown of an electrocardiogram taken September 25, the day after admission. Leads I and III were taken during a respiratory (rate 82), Lead II during an apneic (rate 108) phase. The P-waves vary in form during dyspnea. In these, as well as in the other reproductions of electrocardiograms in this paper, divisions of the ordinates equal 10-4 volts; divisions of the abscissae equal 0.04 of a second. The original curves are sharply contrasted black and white; no half tones are lost by the method of reproduction. They are reduced to three-quarters of the original size.

On October 1, after the administration of 1.5 gm. of digitan in five days, the change from the slow rate during respiration to the rapid rate during apnea became abrupt instead of gradual. During apneic periods a series of ectopic ventricular beats occurs at a rate of 148 per minute (Fig. 2, Lead I) and during transition from apnea to dyspnea various forms of abnormal ventricular complexes (Fig. 2, Leads II and III). A similar phenomenon has been reported by Wassermann.¹ The auricular rhythm is irregular and blocked auricular impulses occur (one follows the fifth ventricular complex in Lead II, and another possible one after the eighth in Lead III). Such an occurrence has been described by Wilson and Robinson.² Three days later while digitan was still being given in daily doses of 0.2 gm. (Fig. 3, Lead III), a photograph of the end of a paroxysm of ventricular tachycardia was secured. The slow rhythm which follows is apparently associated with irregular auricular action

(coarse fibrillation). The amount of digitan was accordingly reduced to 0.1 gm. per diem.

Five days later, on October 10, an extremely slow rhythm during the respiratory phase made its appearance (Fig. 4, Lead II); digitan was discontinued altogether. With the first respiratory movement (Fig. 4, upper strip) the cardiac cycle begins to lengthen. Increase in the P-R intervals begins at the same time. At the peak of the

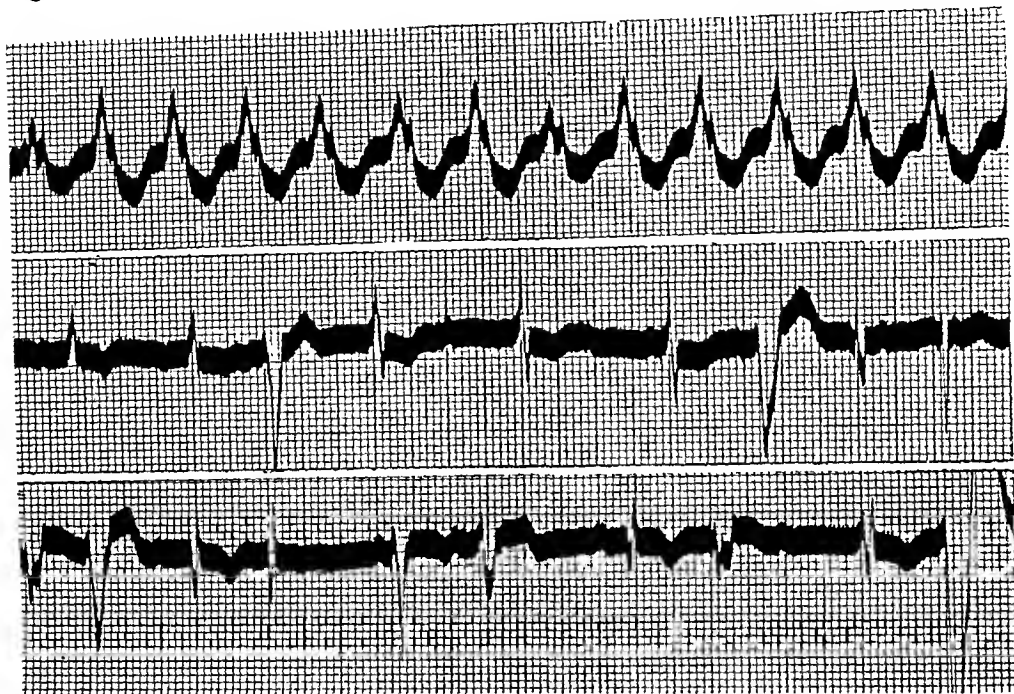


Fig. 2.—The three standard leads in order from above downward are shown of an electrocardiogram taken October 1. Lead I, taken during apnea, shows a series of ectopic ventricular beats (rate 148); Leads II and III, taken during dyspnea, display many different forms of ventricular beats. In Lead II the first and second, in Lead III the seventh ventricular complexes are the only normal ones. These records as well as those in Figs. 3, 4, and 5 were obtained after the administration of digitalis.

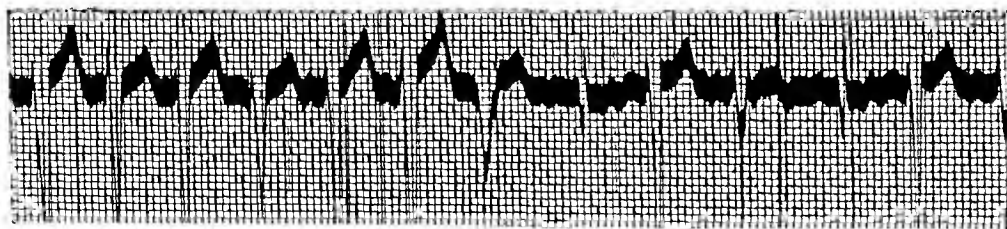


Fig. 3.—Lead III of an electrocardiogram taken October 4 is shown, in which a paroxysm of ventricular tachycardia terminates in a slow ventricular rhythm with auricular fibrillation. This is the only occasion on which auricular fibrillation was observed in this patient.

second inspiration the P-R interval has increased to 0.40 second; in the next cycle auriculoventricular block (2 to 1) is established and continues until the fourth respiration from the last. When the 1 to 1 sequence reappears, the P-R interval (Fig. 4, lower strip) is prolonged (0.25 second) in the first cycle only. The succeeding complexes are evenly spaced; their rate is 115 per minute. P₁, which is usually upright in this patient is inverted except in four instances. Two of them occur during periods of 1 to 1 rhythm, the first of these appearing at the moment of the first respiratory movement; the third introduces normal sequence following a period of incomplete block, the fourth occurs after a premature ventricular beat.

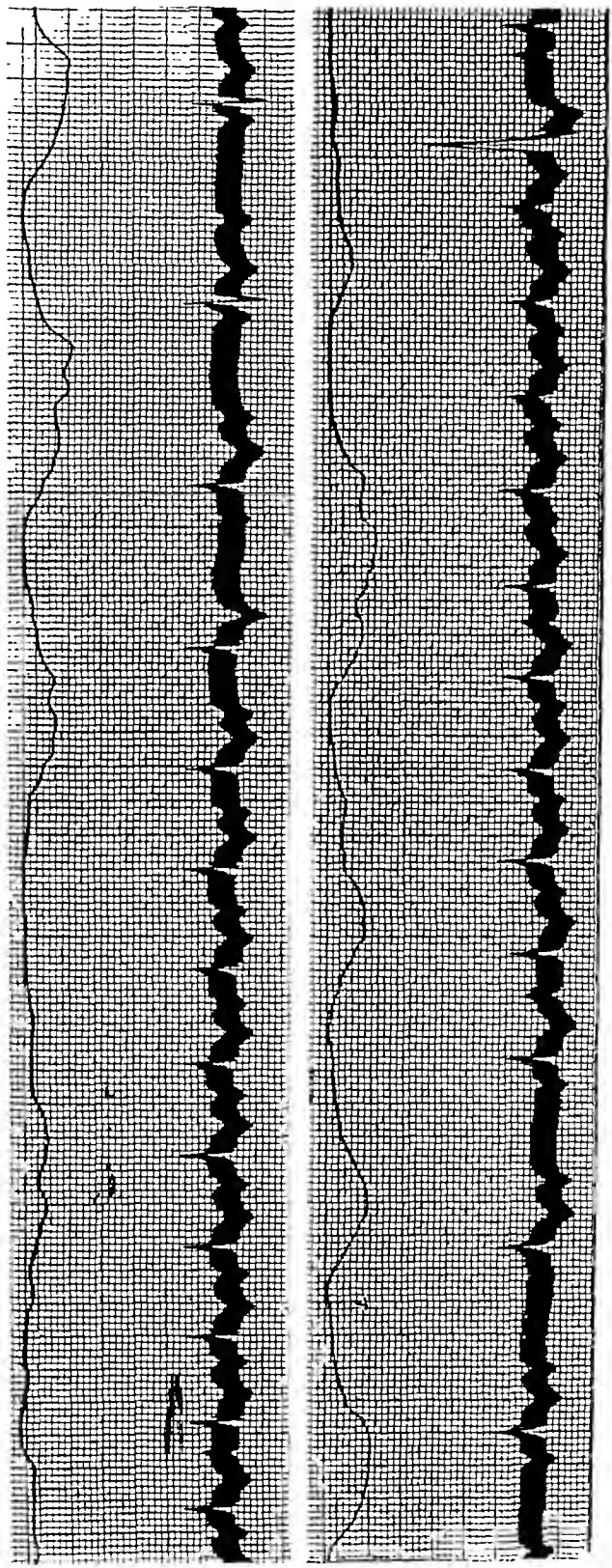


Fig. 4.—Two strips from a continuous record of Lead II during a cycle of Cheyne-Stokes respiration are shown in which the respiratory movements are recorded (inspiration down—expiration up) above the electrocardiogram. The upper strip is taken at the beginning of the respiratory phase, and the first movement appears to be expiratory (the upward movement between the first and second ventricular complexes). An upright P-wave occurs at about this moment. Incomplete block (2 to 1) appears after the second inspiratory movement and persists throughout the respiratory phase, the terminal portion of which is shown in the lower strip. The first P-wave of normal sequence, and one which follows a premature ventricular contraction are upright.

The events which occurred during the period when these electrocardiograms were made have been analyzed (Fig. 6). The curves display the relation of the disturbances of rhythm to the phases of the Cheyne-Stokes cycle. The beginning and the end of each respiration are exactly charted as to time. The height is proportional to the recorded amplitude. It is plain that sinus slowing and respiration begin at the same time. The

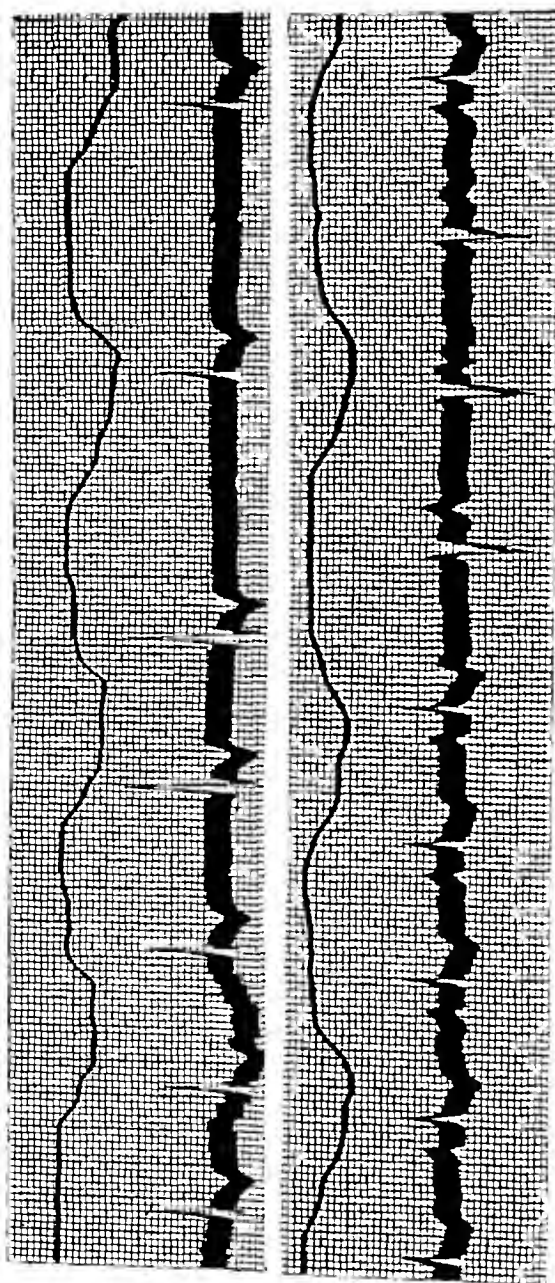


Fig. 5.—Two strips from an electrocardiogram taken October 11 are shown. The upper strip (Lead I) is from a portion of the record just after the beginning of the respiratory phase and shows two independent ventricular contractions (fourth and fifth), the first of which follows a P-wave after an interval of 0.44 second. The two succeeding normal ventricular complexes follow P-waves at intervals of 0.62 and 0.64 second respectively. In the lower strip (Lead II) the sixth, seventh, and eighth ventricular complexes are abnormal. The T-waves following these vary in form.

auricular rate is reduced from 115 to 104 beats per minute, while the ventricular beats are reduced to one-half the latter figure.

The next day, October 11, the mechanism of the slow rhythm during the respiratory phase was different (Fig. 5). The sinus node usually maintained its function as pacemaker, and the auricular rate was markedly slowed, but at times the ventricles initiated independent contractions (Fig. 5, the fourth and fifth complexes, upper strip). The fifth complex followed the auricular impulse at 0.44 second. The sixth and seventh ventricular complexes which are, however, similar to the usual ones, follow P-waves

after intervals of 0.64 second. As pointed out by Resnik and Lathrop³ all these variations may be explained by the occurrences of impulses originating at different levels in the bundle of His. The appearance of incomplete block was observed only once on this day. Later during the next succeeding respiratory phase three more idioventricular contractions occurred (Fig. 5, lower strip). They are followed by T-waves of such diverse appearances as to suggest the presence of P-waves stimulated by ventricular contractions arriving at the auricles after varying intervals. When these two apparently dissimilar slow rhythms are compared, it appears that in the former (Fig. 4) conduction of impulses from auricles to ventricles is at fault without important change in the rate of impulse formation, while in the latter (Fig. 5), in which marked slowing of the pacemaker appears, various lower portions of the conduction system seem to have taken over the function of originating impulses. Disturbance of conduction is a minor factor but

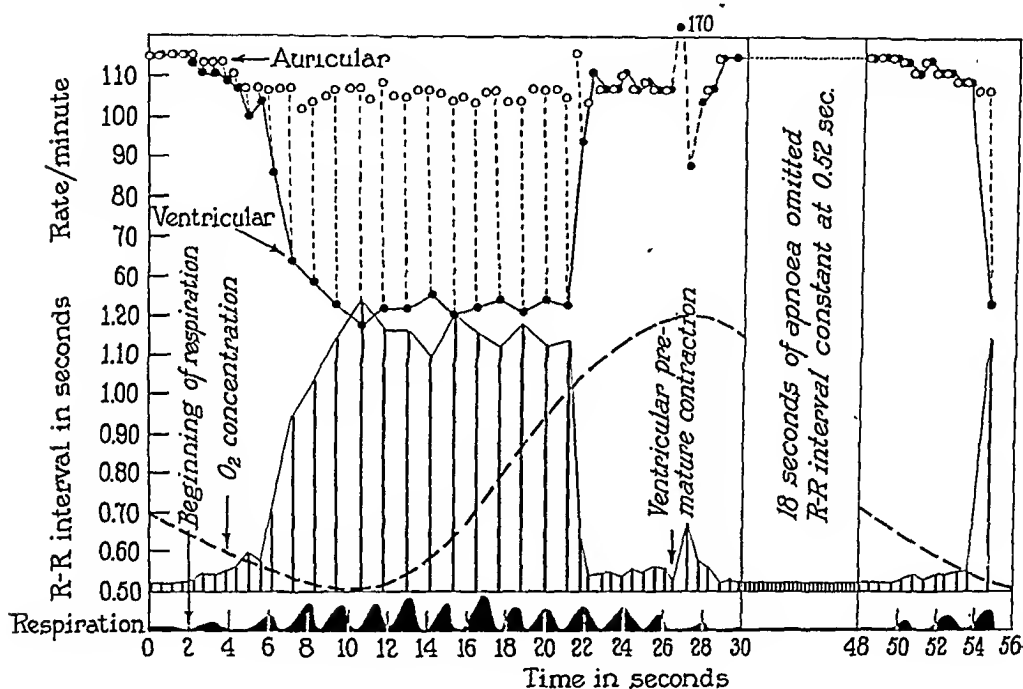


Fig. 6.—This chart shows the relations existing between the electrocardiographic phenomena and the phases of respiration during a little more than one cycle of Cheyne-Stokes breathing. The data were obtained from the continuous tracings of the electrocardiogram and respiratory movements simultaneously recorded on the same film; parts of this record are shown in Fig. 4. The auricular and ventricular rates are plotted in open and closed circles respectively, and those auricular contractions which are succeeded by ventricular beats are joined by broken lines to the ventricular beat which follows them. Ordinates represent time from the arbitrary zero when the chart begins; the particular ordinate upon which a ventricular beat is charted represents, therefore, the sum of all preceding R-R intervals. The curve of concentration of oxygen in the blood, being a curve made from data obtained in a study of other cases exhibiting Cheyne-Stokes respiration (Anthony, Cohn and Steele⁶), is drawn to show probable relations in respect to time only. Rise of the curve from the base line indicates increase in concentration.

contributes an influence on the form of the electrocardiogram. Both these rhythms resemble those which are known, however, to follow stimulation of the vagus nerves; the first exhibiting more especially the effect of stimulating the left, the second, the right vagus (Cohn⁴).

Six days after the administration of digitalis ceased (October 15) all disturbance of rhythm disappeared, leaving only during respiratory periods moderate sinus bradycardia and increase of the auriculoventricular interval from 0.16 to 0.18 second (Fig. 7). One month later, on November 14, after taking 1.6 gm. of digitan in four days, marked slowing of the rate during respiratory periods recurred (40 per minute, Fig. 8).

Again there was marked slowing of the pacemaker. But there may have been more than slowing of the rate of impulse formation, as may be inferred from the difficulty of finding evidence in the electrocardiogram of auricular activity after the third ventricular complex (Fig. 8, lower strip). The formation of impulses may indeed have been suppressed. The next few ventricular contractions would then be idiopathic in nature, but the form of the complex is so nearly identical that this cannot be definitely maintained. On November 15, after giving 0.2 gm. more of digitalin, periods of coupled rhythm appeared, usually during apneic periods but without constant relation to the phases of respiration. Electrocardiograms were taken on November 16 during the exhibition of this rhythm. The inhalation of carbon dioxide exerted no consistent effects. Though cessation of periodic respiration took place, the coupled rhythm was once absent and

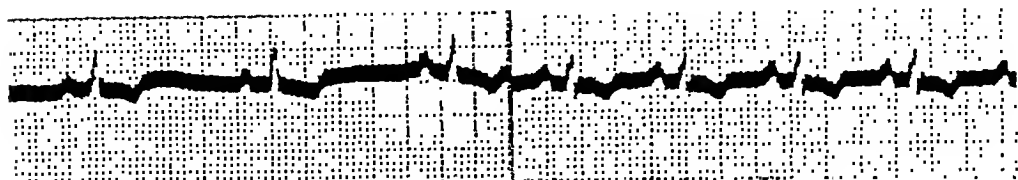


Fig. 7.—Two parts of an electrocardiogram (Lead II) are selected from a continuous record during a single cycle of Cheyne-Stokes respiration on October 15, six days after discontinuing the use of digitalis. The part on the left shows the slow rate during the respiratory phase; that on the right, the rapid rate during apnea.

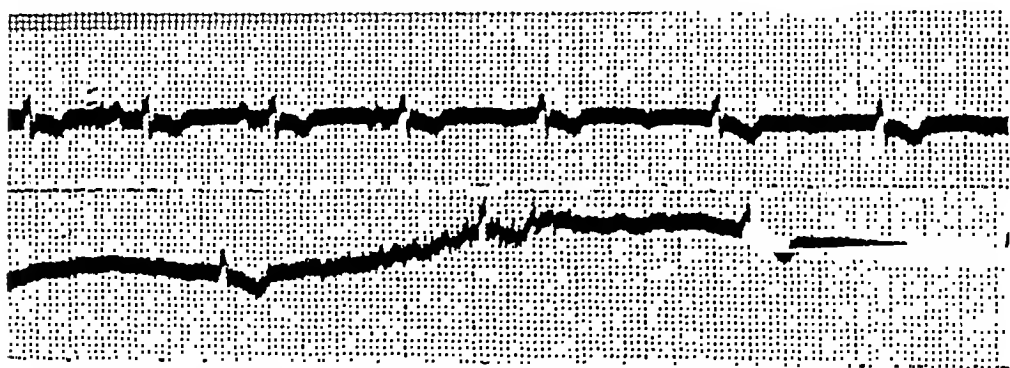


Fig. 8.—An electrocardiogram (Lead II), taken November 14 after the administration of digitalis, is shown. In the upper strip slowing of the rate, change in form of P-wave and increase of conduction time occur as the curve is read from left to right. The beginning of the respiratory phase is in the middle of the strip. The lower strip is continuous with the upper and exhibits extreme slowing of the auricular rate. The rapid oscillations about the fourth ventricular complex are artefacts.

once present. Oxygen administration failed to stop the periods of Cheyne-Stokes respiration, but coupled rhythm was again present at one time and absent at another. The only consistent difference concerned rate. During the administration of oxygen it was 80; during that of carbon dioxide, 100 per minute.

Twenty-four hours before death (November 19) the rhythm returned to normal sequence and constant rate with a somewhat prolonged auriculoventricular conduction time. Cheyne-Stokes respiration also disappeared. The administration of digitalis had been discontinued four days before.

DISCUSSION

This case is similar to that of Resnik and Lathrop in that it presents similar disturbances of cardiac rhythm. In order to analyze the relation of rhythmic and respiratory changes to changes in the composition of the

blood, samples of arterial blood were taken in a manner comparable with that employed by Resnik and Lathrop. The studies of Klein⁵ and subsequent studies of our own⁶ have shown that it is necessary, however, to take many samples in rapid succession during a respiratory cycle in order to secure evidence of the variations which take place in the content of gases. The samples taken in this case showed slight differences only in the concentrations of oxygen and carbon dioxide. An oxygen curve based on the variations found in other cases of Cheyne-Stokes respiration⁶ has, however, been inserted in Fig. 6. This curve is not constructed on the basis of exact quantities, since these differ widely in different cases. The order of magnitude of change in oxygen concentration varied in our studies from 1 to 8 volumes per cent. The time relations between variations in the concentration of gases in the blood and phases of the respiratory cycle were, however, constant. It is with a view to emphasizing these relations that the curve is reproduced. The lowest concentrations of oxygen occur during the early portion of the respiratory phase, the highest during the end of the dyspneic or first part of the apneic phase. The changes in concentration of carbon dioxide occur in inverse relation.

Resnik and Lathrop suggested that periodic anoxemia, occasioned by periods of apnea superimposed upon anoxemia existing as a continuous state due to heart failure with edema, was sufficient to stimulate vagal activity (Greene and Gilbert⁷) and that it was this activity that was responsible for the disturbances of cardiac rhythm. The highest concentration of oxygen which they found occurred, however, during the period of greatest vagus stimulation. Very low concentrations of oxygen (7 or 8 per cent) must, furthermore, be reached before stimulation of the vagus takes place (Greene and Gilbert⁸). But attention must be called to the fact that the action of low tensions applies only to normal cardiac muscle. It is conceivable that diseased heart muscle, such as was present in the patient who forms the subject of the present study, may be more irritable, that is to say more sensitive, to vagal stimulation. Although the lowest concentration of oxygen occurred during the respiratory phase, so that a causal relation may be assumed to have brought on vagal stimulation, the concentrations usually attained do not seem low enough to be per se responsible for the result. The influence of other factors, change in hydrogen-ion content, periodic change in the irritability of the medullary centers or the presence of a drug capable of influencing the tone of the vagus nerves, must be taken into account. The last factor, digitalis, was present both in the case of Resnik and Lathrop and in our own. In our own, furthermore, extreme slowing, auriculoventricular block, appearance of idioventricular complexes, paroxysms of ventricular tachycardia and coupled rhythm were all present only while the patient was under the influence of the drug.

Many statements concerning the fact that change of rate and rhythm of the heart take place with the changing phases of Cheyne-Stokes respiration are to be found in the literature. Reports of illustrative cases, however,

are not numerous. The first two were reported by Gallavardin⁹ in 1910 and 1911. He thought that the slow rhythm was due, in the first case, to incomplete auriculoventricular block (2 to 1), and in the second to coupled rhythm in which every second beat failed to cause pulsation at the wrist. He states that both of these rhythms occurred only while the patients were under the influence of digitalis.

Bäumler¹⁰ in 1912 reported a case of heart failure in which Cheyne-Stokes respiration following a dose of morphia by less than twenty-four hours was observed fifteen days before death. During the height of the period of respiration on several occasions complete cessation of ventricular activity occurred, once for fifteen seconds: "Herzstillstand" was accompanied by a veritable Stokes-Adams syndrome. This patient, too, had received digitalis for a long period of time.

Roth¹¹ in 1916, included reports of several very interesting cases in a treatise on the effect of Cheyne-Stokes respiration on irregular action of the heart. In two cases of auricular fibrillation, marked slowing during the respiratory phase occurred. Atropin employed in one relieved slowing without affecting the periodicity of the breathing. Two cases with coupled rhythm exhibited marked slowing with dyspnea. One of these had been given digitalis; there is no mention of the use of the drug in the other case. The most interesting of all of his observations was that made after prolonged exhibition of digitalis in a patient with heart failure but without Cheyne-Stokes breathing. On walking about the room, dyspnea of sufficient degree occurred to bring on auriculoventricular block. Roth demonstrated this occurrence by means of simultaneous tracings of the jugular and apical pulses.

In 1925, Resnik and Lathrop's report appeared. Their patient too had received considerable digitalis. This was the first published electrocardiographic record of auriculoventricular block occurring during the respiratory phase of Cheyne-Stokes breathing. Fischer¹² in 1927, described a patient suffering from auricular flutter in whom during the period of apnea, flutter with or without incomplete heart block (2 to 1) was transformed into heart block, the ratio being 7 to 1 or even 8 to 1 during the respiratory phase after the administration of only 0.1 gm. of digitalis, an amount which seems too small to be of significance. Wenckebach¹³ mentions a case of bigeminy, and Wassermann¹ two cases with ventricular tachycardia occurring during the period of apnea, in all three of which a great reduction in rate during the respiratory phase actually was apparent, but since they were used only as illustrative cases, no mention of therapy was made.

In thirteen cases in which great slowing in rate and disturbance of the basic cardiac rhythm took place during the dyspneic phase of Cheyne-Stokes respiration, nine had received considerable amounts of digitalis; in three, no mention of the use of the drug was made; in one, only 0.1 gm. of digitalis was given. In one case with heart failure, after prolonged use of

digitalis, a sudden attack of dyspnea induced a very slow rhythm. In view of the recognized effect of digitalis on the behavior of the vagus nerves, its presence in the organism must be considered as a potent influence in enhancing the strength of periodic vagal stimulation during Cheyne-Stokes respiration whether due to change in the center itself or to rhythmic deficit of oxygen.

SUMMARY

1. A case of heart failure is reported exhibiting Cheyne-Stokes respiration in which various types of cardiac arrhythmia were recurrently manifested during the dyspneic phases of the respiratory cycle.

2. Sinus slowing, prolongation of the P-R interval, partial and complete heart-block, and during suppression of the formation of sinus impulses, idiopathic ventricular rhythms were observed.

3. All of these changes in rhythm have previously been observed to follow various degrees of vagal stimulation.

4. With the exception of sinus slowing, all the phenomena occurred only after administration of digitalis in effective therapeutic doses.

5. Since digitalis has usually been administered in cases of Cheyne-Stokes breathing in which such disturbances of rhythm appeared during the dyspneic phase, it is suggested that the vagal effect of this drug is a powerful adjunct in their production.

Since this paper was prepared for publication, two articles dealing with reports of somewhat similar cases have come to our attention. Hamburger, W. W., Katz, L. N., and Rubinfield, S. H.: *AM. HEART J.* 7: 498, 1932; and von Hoesslin, H.: *Klin. Wchnschr.* 11: 971, 1932.

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THE ELECTROCARDIOGRAPHIC CHANGES FOLLOWING THE LIGATION OF THE SMALL BRANCHES OF THE CORONARY ARTERIES*

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THE occurrence of a negative T-wave in the electrocardiogram following the experimental ligation of the coronary arteries in the dog was first observed by Kahn¹ in 1911. Smith² in 1918 described a series of successive changes in the electrocardiogram following the ligation of these vessels. In this investigation sixty-six dogs were used. The right coronary artery was ligated in eight, the anterior descending branch of the left coronary artery in eleven, the circumflex branch of the left coronary artery in fourteen and a combination of the various branches of the latter two vessels in thirty-three animals. Forty of these dogs survived the operation and were observed for periods ranging from two to ninety-one days. These observations were later checked in a series of twenty dogs in which various divisions of the anterior descending and circumflex branches of the left coronary artery were ligated.³ Sixteen of this series recovered from the operation. Electrocardiograms were taken prior to the operation and in the vast majority at daily intervals during the first week to ten days of the postoperative course. After this period, records were obtained at one- to two-week intervals until the animal was sacrificed. The alterations in the electrocardiogram subsequent to the closure of the branches of the left coronary artery were successive and quite uniform in character. Soon after the ligation of either of the main branches of the left coronary artery the T-deflection became more prominent and in some instances approached, or even exceeded, the height of the R-deflection. Occasionally, the entire R-T segment was involved and arose from the descending limb of the R-wave well above the iso-electric line. The initial change in the electrocardiogram seemed to vary with the extent of the functional impairment of the myocardium. It was always greatest following the closure of either of the main branches of the left coronary artery, particularly the circumflex, and was most marked after a combined ligation of these vessels. This alteration might furthermore be magnified by increasing the work of the heart through the constriction of the aorta.

Within twenty-four hours the T-deflection became negative. The sharp character of the T-wave in the downward or even in the later upright position was a distinctive feature. The extent and duration of the

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negative T-deflection in general varied with the size of the vessel ligated and possibly with the degree of the collateral circulation. In the animals in which the small branches were ligated the above alterations occurred in Lead I or in Leads I and II, whereas following the closure of either of the main branches of the left coronary artery it frequently appeared in all leads. The extent of the downward deflection gradually became less, and by the sixth to eighth day, or even in less time, changed to a positive phase in Lead III and later in Leads II and I. Occasionally the order was reversed in which the T-wave in Lead I became positive first, followed by a similar alteration in Leads II and III. These successive changes frequently continued until the T-wave was upright in all leads or at least in two derivations. This stage was usually observed in the second and fourth week and was often associated with a reduction in the amplitude of the R-deflection. Thereafter the rate of progression was much slower. In some the T-wave returned to the iso-electric line or even to a negative phase following which there was apparently no further alteration. Instances were recorded in which the T-wave was distinctly negative in all leads thirty-eight days after the ligation of the anterior descending branch of the left coronary artery. In other animals similar findings were observed in Leads II and III when sacrificed fifty to seventy days after the operation.

A reduction in the amplitude in the QRS group was observed by Smith, but not emphasized until a later report.⁴ It was pointed out that this alteration followed a closure of the circumflex branch of the coronary artery in six (100 per cent), the anterior descending branch of the left coronary artery in two (20 per cent) and a combined ligation of the branches of these arteries in four (30 per cent). This change was observed as early as the second day. In some the amplitude returned to the original level, whereas in others it persisted until necropsy. The latter was noted particularly in the animals in which the circumflex branch was ligated. There was occasionally some slurring of the QRS group, but no distinctive increase in the duration of these complexes.

In the above investigation, premature contractions were often noted a few minutes following the ligation and were frequently present twenty-four to forty-eight hours after the operation. They occasionally occurred in runs and in some instances passed into a tachycardia which terminated in ventricular fibrillation and death. One animal with the circumflex branch of the left coronary artery ligated was cited which had many premature contractions throughout the postoperative period, and on two occasions was observed during paroxysmal tachycardia of ventricular origin. Lewis⁵ previously had produced paroxysmal tachycardia by the ligation of the coronary arteries and this condition has since been encountered in man following coronary occlusion.

The experiments of Hamburger, Priest and Bettman⁶ were similar in many respects to the investigations of Smith. These observers were

primarily interested in the occlusion of the smaller arteries and the production of a disseminated fibrosis of the myocardium in the dog through the introduction of a suspension of lycopodium spores into the coronary circulation. In some instances, however, the larger branches of the left coronary artery were completely filled, producing extensive areas of infarction comparable to that induced by the ligation of these vessels. Furthermore, the animals were studied electrocardiographically in much the same manner as in the ligation experiments. The electrocardiograms of the dogs that received overwhelming injections of the lycopodium suspension and died within a few minutes or during the first twenty-four hours showed conspicuous alterations in the T-deflection and in the R-T segment. In the animals which survived the injections for weeks or even months the successive changes in the T-wave were similar to those observed following the ligation of the coronary arteries. When the injection missed the lumen of the vessel "no permanent change in the electrocardiogram was found, although strange and curious findings were noted transitorily" which they attributed to trauma and hemorrhage produced by the manipulation.

Barnes and Mann⁷ have more recently reported a series of experiments on twelve dogs in which the pericardium was opened in six, a posterior division of the circumflex branch of the left coronary ligated in three, and one or more branches of the right coronary artery ligated in three animals. They observed that the opening of the pericardium without further operative procedure produced successive changes in the T-wave and noted a significant deviation of the RS-T segment following the ligation of the branches of the right and left coronary arteries. The deviations in the RS-T segment, involving particularly Leads I and III, appeared immediately after the ligation and disappeared within twenty-four hours. Thereafter the alterations in the electrocardiogram concerned chiefly the T-deflection which passed through a series of changes similar to those previously described. While the RS-T segment deviations resulting respectively from the ligation of the branches of the right and left coronary arteries differed somewhat in their general character, the most important aspect concerned the direction assumed in Leads I and III. Following the ligation of the branches of the right coronary artery they were down in Lead I and upright in Lead III, whereas subsequent to the closure of a division of the left coronary artery, the reverse order prevailed. These investigators concluded that the RS-T segment deviations were distinctive for lesions of the right and left ventricle, but did not feel that the changes in the T-wave were necessarily indicative of a cardiac infarction, since this alteration was observed after the opening of the pericardium without the ligation of a vessel.

Otto,⁸ Wood and Wolferth,⁹ and Feil, Katz, Moore, and Scott¹⁰ have

studied the early electrocardiographic changes following the closure of the coronary arteries in the dog. Otto observed a negative T-deflection with an ST fusion in Lead II immediately after the closure of the right coronary artery and an increase in the amplitude in the T-wave with a disappearance of the RT interval following ligation of the main division of the left coronary artery. Feil, Katz, Moore, and Scott ligated only the anterior descending branch of the left coronary artery. They concluded that the ligation of this vessel, in acute experiments, produced no characteristic RT deviation in the electrocardiogram, provided the cardiac mechanism remained normal. In further experiments, however, in which in addition to the closure of the above vessel the inferior vena cava was ligated for periods of five minutes, the typical alterations appeared. Wood and Wolferth, on the other hand, recorded definite alterations in the electrocardiogram following the temporary closure of various branches of the left coronary artery. In some instances an inverted T-deflection was the initial change, whereas in other experiments the opposite effect was produced; *viz.*, an elevation of the RT segment. These alterations disappeared soon after the clamp was removed from the vessel. The magnitude of the above changes seemed to depend on the vessel ligated, the extent of the infarction, and the duration of the occlusion. The ligation of the circumflex branch of the left coronary artery was more effective in producing the changes in the electrocardiogram. The most striking alterations, however, were observed following the combined ligation of the circumflex and the anterior descending branches of the left coronary artery. The size of the area of infarction and the extent of the functional impairment of the myocardium seemed to be the most important factors.

Clinical application of these experimental findings have been made by numerous observers and in those instances in which the initial electrocardiograms were taken soon after the cardiac accident and progress curves obtained at frequent intervals, the alterations agreed in every essential detail with those produced experimentally in the dog.^{11, 12, 13, 14, 15, 16} The changes in the T-deflection duplicate those encountered in the experimental curves except for more rapid progression in the latter. The alterations pertaining to the reduction in the amplitude in the QRS group were likewise of the same general character. The greatest difference concerned the initial change in the electrocardiogram or the so-called R-T deviation. This feature was distinctly more prominent and lasting in the clinical electrocardiogram. This, however, is not unexpected in that the condition of the coronary arteries in the dog is not comparable to that ordinarily found with coronary occlusion. In the latter, because of the associated sclerosis of the coronary arteries the derangement of the myocardial function is likely to be more profound and the reparative process slower than that in the dog following

the closure of a corresponding vessel. There is, furthermore, a greater possibility of an extension of the myocardial damage, as indicated by Parkinson and Bedford¹⁵ and as suggested by certain curves observed by the writers.

Alterations in the T-deflection have been produced experimentally by other means and have been observed clinically in conditions in which the coronary arteries were at least not primarily concerned. Eppinger and Rothberger,¹⁷ in 1909, noted a negative T-wave following the injection of silver nitrate into the right basal portion of the heart, whereas an exaggerated deflection was obtained when the chemical was introduced into the left apical region. The opposite effect was induced by spraying the heart with ethyl chloride. Wilson and Herrmann¹⁸ and Smith³ also observed that localized temperature changes alone produced striking alterations in the T-deflection. Wilson and Finch¹⁹ obtained similar results in man by having the subject drink ice water. Parade and Stepp²⁰ injected 40 per cent lipiodol solution into the myocardium through the intact chest wall and found that the T-wave became negative within twenty-four hours and in most instances subsequently returned to the original level. Porte and Pardee²¹ observed three cases of rheumatic pericarditis with a negative T-wave in Leads I and II and at necropsy in one found an early fibrotic lesion with moderate cellular exudate beneath the epicardium. Similar electrocardiographic changes were noted by Scott, Feil, and Katz²² in pericarditis with effusion. They also produced an alteration in the S-T segment and in some instances an inversion of the T-wave by the experimental introduction of fluid into the pericardial sac.²³ These results were attributed to the increased pressure on the heart and a consequent anoxemia. Cohn and Swift²⁴ recorded changes in the T-deflection during rheumatic fever which were regarded as being indicative of a myocardial involvement. These findings have since been confirmed by other observers. Suggestive alterations of the same general character have also been encountered during the course of pneumonia,²⁵ diphtheria, and scarlet fever.²⁶

Recently Crawford, Roberts, Abramson, and Cardwell²⁷ have studied the effects of localized ventricular lesions on the electrocardiogram in the cat. These lesions were produced by electric cautery and were about $\frac{1}{2}$ cm. in diameter and as deep as possible without penetrating the ventricular cavity. In order to facilitate the interpretation of their results, the ventricular wall was divided into eight regions, the left apex anterior, the left base anterior, the left apex posterior, the left base posterior, the right apex anterior, the right base anterior, the right apex posterior, and the right base posterior. These observers concluded that lesions in similar sites produced the same type of curve. Lesions on the anterior surface of the left ventricle gave a T₁ type of electrocardiogram, whereas those on the posterior surface of the left ventricle

including the apex produced the T_3 type. Cauterization of the right ventricle at the various sites indicated above, except possibly the anterior base, resulted in a curve of the T_3 type.

The ligation experiments so far recorded have been concerned for the most part with the larger branches of the coronary arteries. In the present investigation only the smaller surface branches were ligated in order to determine whether the closure of a vessel of this size would produce characteristic alteration in the electrocardiogram. The vessels selected on the left ventricle were usually the third or fourth subdivisions and a ligation was made a short distance proximal to their penetration of the myocardium. The influence of certain stages in the operative procedure on the electrocardiogram was also studied. It was hoped that these results might be helpful in the diagnosis of the occlusion of the smaller coronary arteries in man.

In this study, thirty-seven experiments were performed on twenty-four dogs. Five of these animals were subjected to two operations and four animals to three operations. The dogs were anesthetized with ether; a tracheal cannula was inserted and the anesthesia continued under positive pressure.

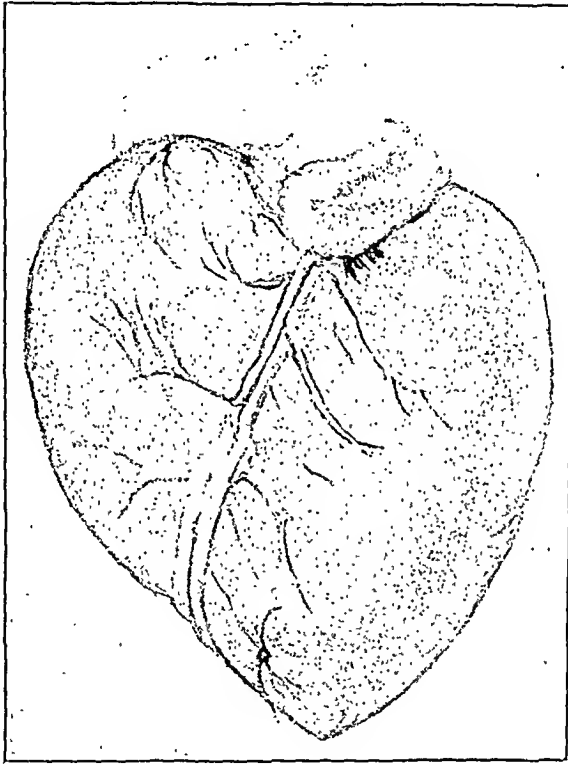
The chest wall was opened by an incision parallel to the sternum on either the right or left side, depending on which ventricle was to be exposed. In four instances the chest wall was immediately closed without further operative procedure. In seven dogs the operation was extended to the pericardium and an incision made to the same extent as in the ligation experiments. Sterilized vaseline was applied between the visceral and parietal layers of the pericardium in three animals in order to prevent adhesions. The opening in the pericardium was sutured with plain catgut and the chest was closed in the usual manner. In the remaining twenty-six experiments a small vessel was ligated. The opening in the pericardium was made as nearly as possible over the point selected for the ligation and a silk ligature passed under the artery and periarterial structures. In the five instances in which a posterior division of the left coronary artery was ligated, the incision in the pericardium was made directly over the vessel in two and on the lateral aspect of the left ventricle in three.

One dog died from pneumonia and one from an intrapleural hemorrhage eight days following the operation. The remaining twenty-two animals were autopsied at chosen intervals from one to sixty-two days after the operation.

An electrocardiogram was taken prior to the anesthetic and at daily intervals following the operation. In the first eight experiments curves were taken after the anesthetic, and at frequent intervals during the first few hours after the operation. The anesthetic produced no significant alterations in the electrocardiogram. During the early post-

operative period, various types of arrhythmias were observed, and in a few an elevation of the T-wave was noted. The skin resistance was measured in each instance and never exceeded 2500 ohms.

A small twig of the anterior descending branch of the left coronary artery was ligated in eleven dogs. In one instance in which progress curves were taken at frequent intervals following the operation, an increase in the amplitude of the T-deflection was noted thirty minutes after the ligation. In another, Fig. 1, the T-wave in Leads I and II was negative within three hours. Within eighteen to twenty-four hours



4

Fig. 1.—Dog 2. *Operation:* Ligation of a small branch of the coronary artery on the anterior surface of the left ventricle. *Results:* Inversion of the T-wave in all leads followed by an increased amplitude and later by a return to the normal level. R-T segment elevated. *Pathology:* Twenty-nine days postoperative. Adherent pericardium, occlusion of a coronary vessel, and subepicardial fibrosis on the anterior surface of the left ventricle. Microscopic examination showed subpericardial fibrosis with extension into the adjacent myocardium.

a downward deflection of the T-wave in two or more leads was recorded in eight dogs. This alteration was possibly obscured in one instance by a persistent ventricular arrhythmia. In the remaining two animals there were no significant changes in the electrocardiogram. The location of the ligation and the leads in which the negative T-deflection occurred in the eight animals is shown in Fig. 2. It is to be noted that the T-wave was down in all leads in four, in Leads II and III in one, and in Leads I and II in three animals.

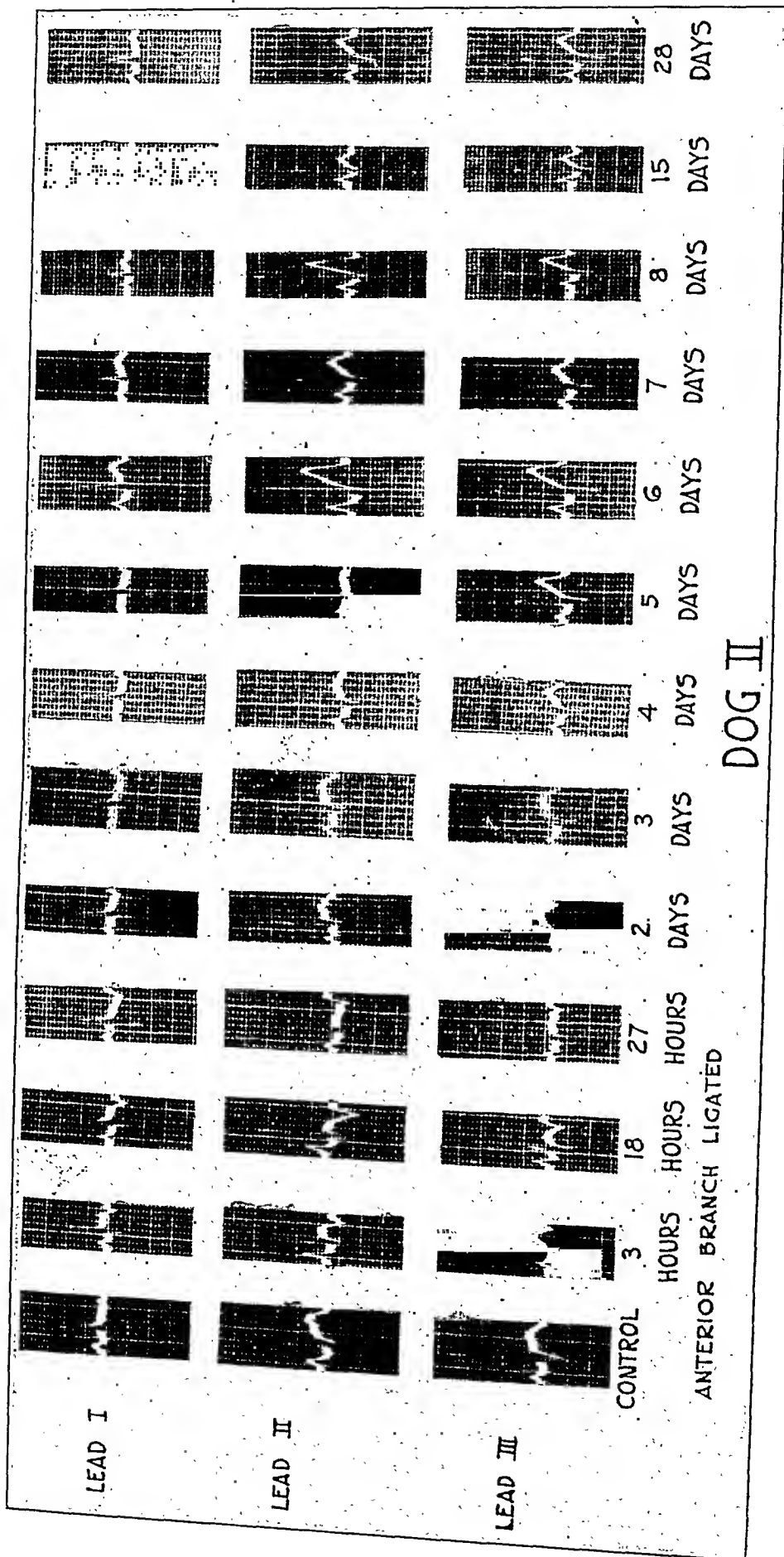
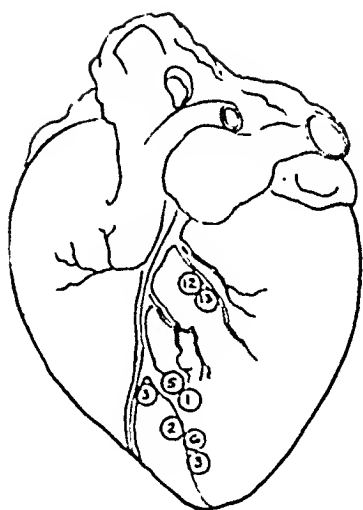
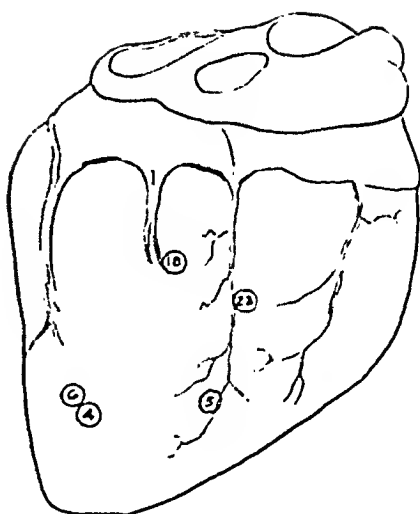


Fig. 1 B.—See legend under Fig. 1 A.



ANTERIOR

Fig. 2.

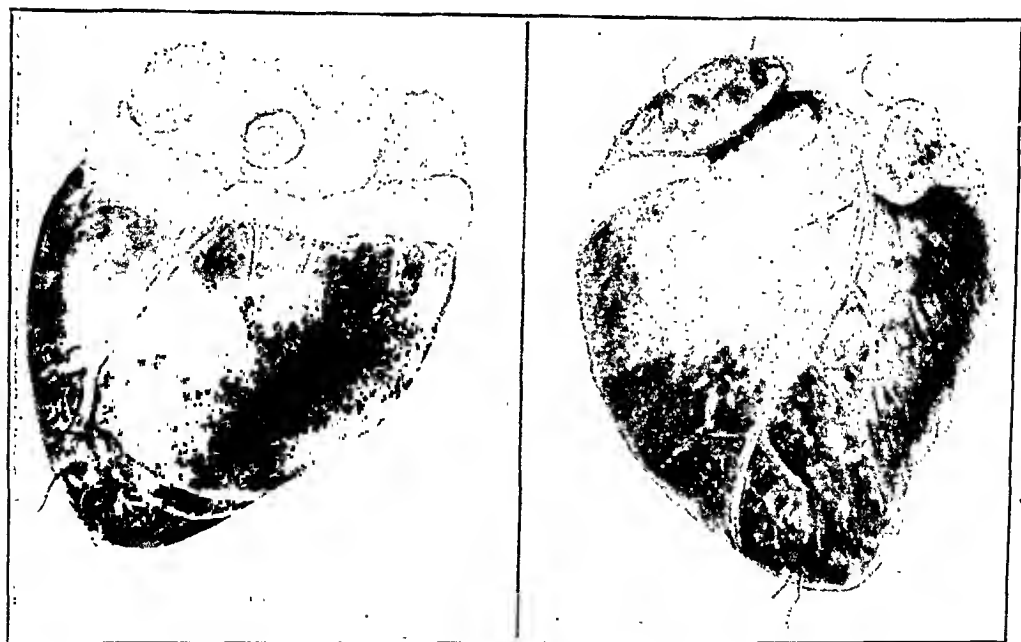


POSTERIOR

Fig. 3.

Fig. 2.—Anterior surface of left ventricle showing site of ligation for each animal. Inversion of T_1 and T_2 followed in Dogs 3 (twice) and 5. Inversion of T_2 and T_3 followed in Dog 12. Inversion of T_1 , T_2 , and T_3 followed in Dogs 1, 2, 6, and 11.

Fig. 3.—Posterior surface of left ventricle showing site of ligation for each animal. An inverted T-wave in all leads occurred in each instance.



A

B

Fig. 4.—Dog 6. *First Operation:* Ligation of a small coronary vessel on the posterior surface of the left ventricle. *Result:* Inversion of T-wave in all leads with a high take-off of the R-T segment. *Second Operation:* Ligation of a small branch on the anterior surface of the left ventricle. *Result:* Inversion of the T-wave in all leads with an elevated R-T segment. *Pathology:* Seven days postoperative. Adherent pericardium over both ligations and occlusion of both vessels. Microscopic examination showed degeneration of the muscle fibers and partial replacement by connective tissue.

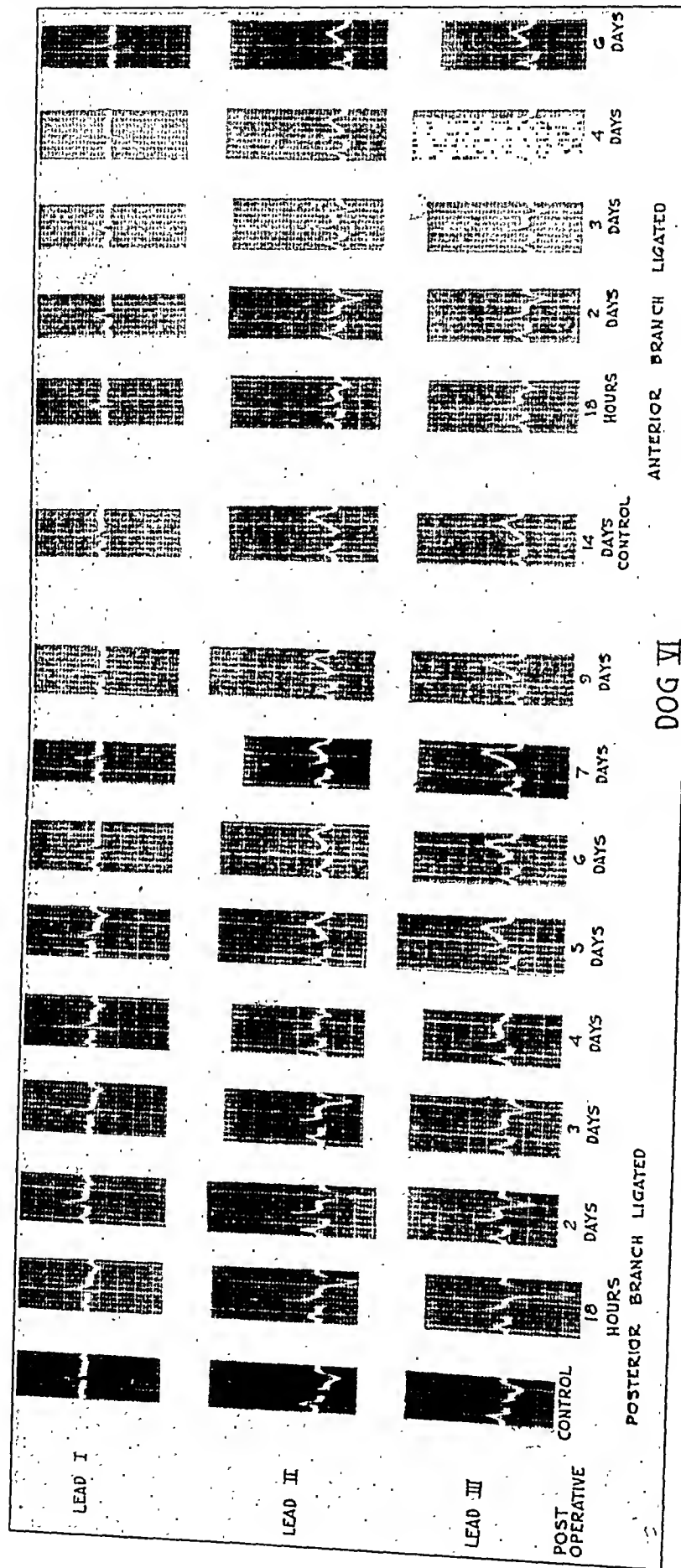


Fig. 4 C.—See legend under Fig. 4 A and B.

The T-wave usually returned to the positive phase in from four to six days. The change to the upright position was observed first either in Lead I or in Leads II and III. This was followed by a gradual increase in the amplitude of the T-deflection which reached the greatest height between the fifth and ninth day following the ligation, and gradually returned to the original level. The increase in the amplitude of the T-deflection was most prominent in Leads II and III, even though it was not always preceded by a negative phase in these particular derivations.



A

Fig. 5.—Dog 15. *Operation*: Ligation of small descending branch of coronary artery on right ventricle. *Result*: Inverted T-wave in Leads II and III, return to a positive phase on second day, followed by an increase in amplitude. R-T segment elevated. *Pathology*: Six days postoperative. Adhesions between pericardium and epicardium. Whitish discoloration of endocardium and small whitish areas in the myocardium below the ligation. Microscopic examination: Muscle bundles shrunken with loss of fibrillae and nuclei. Cytoplasm granular and vacuolated. Granulation tissue in epicardium.

A vessel was ligated on the posterior surface of the left ventricle in five dogs. These vessels were divisions of the circumflex branch of the left coronary artery. The ligation of these arteries produced the most constant change in the electrocardiogram, since in every instance a negative T-deflection in all leads was observed within eighteen hours (Fig. 3). The subsequent changes in the T-deflection after ligation of a posterior branch were identical to those following the ligation of the

divisions of the anterior descending branch of the left coronary artery. In three dogs the T-wave returned to the positive phase by the fourth day and the remaining animals were autopsied at twenty-four to forty-eight hours respectively after the operation in order to observe the pathological changes during this period of the T-wave negativity. In Fig. 4 it will be observed that after a period of fourteen days a vessel on the anterior apical surface of the left ventricle was ligated. The

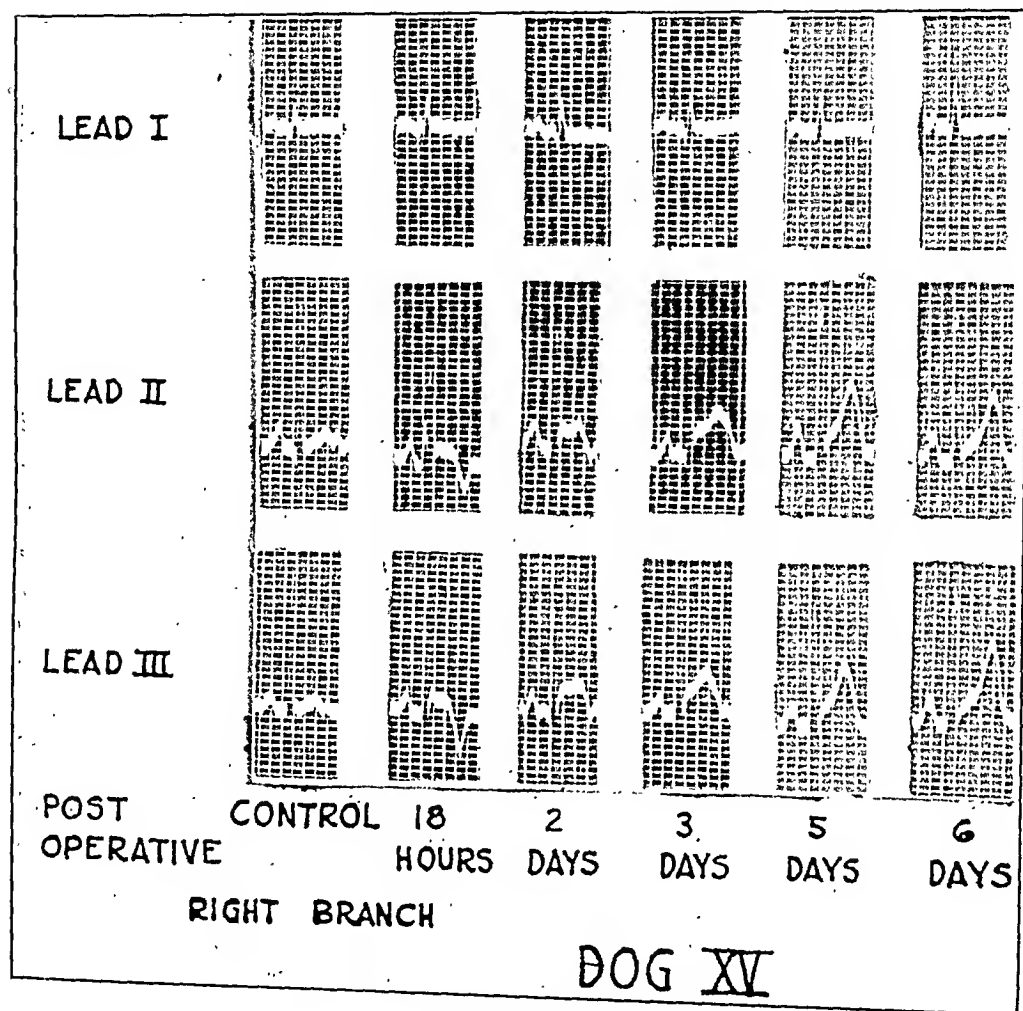


Fig. 5 B.—See legend under Fig. 5 A.

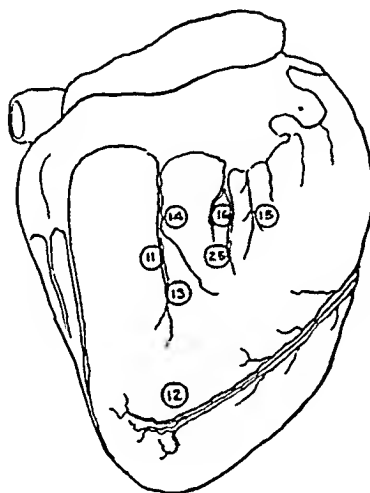
alteration in the T-wave following the latter ligation is of the same general character, but less marked.

In eight dogs a branch of the right coronary artery on either the anterior or lateral surface of the right ventricle was ligated. A negative T-wave occurred in seven dogs. This appeared in Lead I alone in four, and in Leads II and III in three (Fig. 5). These results seemed to differ from those observed following the ligation of the branches of the left coronary artery only in that the T-negativity was more frequently confined to Lead I, and under these circumstances persisted throughout the

period of observation. The location of the ligation and the changes in the T-wave associated with each are indicated in Fig. 6.

The pericardium was opened and sutured without the ligation of a vessel in seven dogs. A negative T-wave was reported in six and occurred in all leads in three animals (Fig. 7). Although the application of vaseline prevented the formation of adhesions between the layers of the pericardium, alterations of the electrocardiogram occurred. In all instances in which the animal was followed for any considerable period the electrocardiogram returned to normal as in the ligation experiments.

The chest wall was opened in four dogs without further operative procedure. In one instance the T-wave became negative in Lead I. This



RIGHT

Fig. 6.—Right ventricle, showing site of ligation for each animal. Inversion of T_1 alone occurred in Dogs 11, 13, 14, and 16. Inversion of T_2 and T_3 occurred in Dogs 12, 15, and 25.

animal was autopsied on the fourth day and an extensive pericarditis was found. There were no significant electrocardiographic changes in the remaining three animals.

In those animals in which the pericardial sac was opened, but no vessel ligated, an inflammatory reaction of the visceral layer with a whitish discoloration of the underlying epicardium was found. Adhesions were present between the pericardium and the chest wall and between the pericardium and the epicardium in most cases. Even though there were no adhesions, the discoloration of the epicardium was a constant feature. The larger vessels passing through this area were patent in all instances.

On microscopic examination an inflammatory reaction was found in the pericardium and epicardium which extended into the superficial muscle tissue. The muscle cells in the involved area were lightly stained

and showed fragmentation and vacuolization. Varying degrees of cellular infiltration were present with some separation of the muscle fibers. There was also a marked hyperemia with an engorgement of the capillaries, and in certain instances hemorrhagic areas.

In the ligation experiments examination of the heart at necropsy showed that the vessel was occluded in every animal. The gross changes in the myocardium at the site of the infarction were usually slight and difficult to detect. In some there was no apparent alteration in the appearance of the cardiac musculature. Even in those instances in which gross changes were present it is extremely doubtful if many of the lesions would have been located had not the ligature directed attention to them. These lesions were usually limited to the central por-

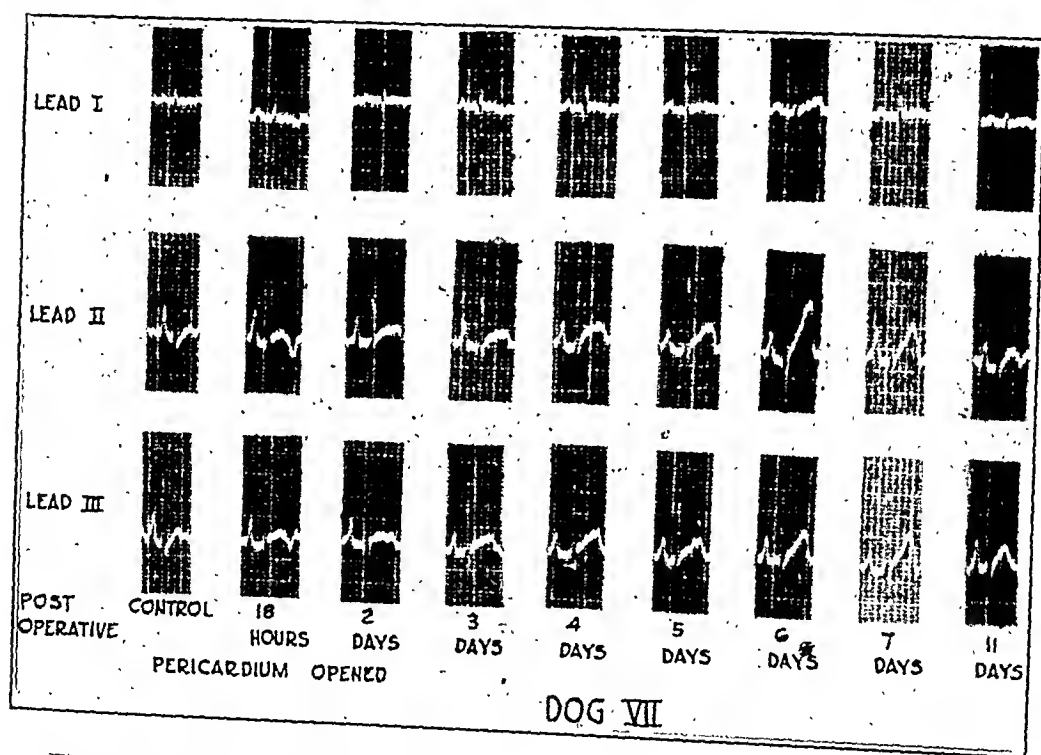


Fig. 7.—Dog 7. Operation: Pericardium opened and sutured without disturbing the myocardium. Result: Inversion of the T-wave in all leads with elevation of the R-T segment followed by an increased amplitude of the T-wave. Pathology: Eleven days postoperative. Thickened and adherent pericardium with the underlying vessels patent. Microscopic examination showed fusion of the pericardium and epicardium by connective tissue. The adjacent muscle cells stained poorly and contained vacuoles.

tion of the ventricular wall, but occasionally extended to the endocardium. In only one animal was there a distinct thinning of the ventricular muscle. The microscopic changes varied with the age of the lesion. In dogs autopsied twenty-four to forty-eight hours after the ligation, the histological changes were those of an acute degenerative process consisting of a loss of cellular outline and striations, indistinct nuclei, the presence of vacuoles in the cells and a cellular infiltration.

Fibrous tissue replacement generally began by the fifth to seventh day and was usually fairly completed by the end of the second or third week.

COMMENT

In the present investigation the changes in the T-wave were the most characteristic features. They occurred following the ligation of the smaller branches of the coronary arteries, after an incision in the pericardium, and in one instance subsequent to the opening of the chest wall alone. The various stages in the evolution of these alterations were associated with fairly definite pathological findings. Histological examinations during the period of negative T-deflection showed an acute degenerative lesion in the ligation experiments and an active inflammatory reaction in those in which an opening was made in the pericardium. When sections were made after the T-wave had returned to the positive phase or an exaggerated upright position, the histological picture was that of a healing process with fibrous tissue formation. The return of the electrocardiogram to the normal was associated with complete replacement by fibrous tissue.

It is to be noted from Figs. 2, 3, and 5 that there is no apparent correlation between the location of the lesion and the type of the electrocardiogram. In each instance in which a vessel was ligated on the posterior surface of the left ventricle, the T-wave became negative in all leads. The closure of a vessel on the anterior surface of the left or right ventricle might be followed by a negative T-deflection in all leads, in Leads II and III or on the right side in Lead I alone. In those in which the ligation of a posterior branch was followed after a period of two or three weeks by the closure of an anterior branch of the left ventricle there was no particular difference in the T-negativity except that it was more marked with the posterior lesion.

The changes in the R-T and the S-T segments were not a prominent feature. They occurred in the pericardial experiments as well as in those in which a vessel was ligated. When present they were invariably overshadowed by the alteration in the T-deflection and apparently dependent on the latter. Within recent years the alterations in the electrocardiogram associated with coronary occlusion have almost exclusively been referred to as an R-T deviation. In view of the findings in the dog where it is possible to follow each successive stage in the evolution of these changes we are not convinced that this is the correct interpretation. On the other hand, it would seem that the T-wave is primarily concerned and that the alterations in the R-T segment are secondary to the latter manifestations.

The alterations in the T-deflection, although less prominent and of shorter duration, were of the same general character, and the successive changes were identical to those described by Smith and later con-

firmed by various investigators of coronary occlusion. It is to be recalled that the lesions in the myocardium produced by the ligation of vessels in our experiments were very small and in certain instances not apparent in the gross specimen. Myocardial lesions were also demonstrated by the histological examination in each of the six animals in which alterations in the electrocardiogram occurred after an incision in the pericardium. In the one dog in which the T-wave changed to a negative deflection after the opening of the chest wall an extensive pericarditis was found at necropsy. While sections were not made of the heart in this particular instance, we are justified in assuming, in view of the findings in the other experiments, that the myocardium was involved. With this possible exception the successive changes in the T-wave were associated with a demonstrable lesion of the myocardium. It is believed that this type of electrocardiographic alteration is indicative of myocardial damage and that the changes observed by Barnes and Mann⁷ after the opening of the pericardium, are explained on this basis. This is in accord with the observations of Porte and Pardee²¹ with reference to rheumatic pericarditis and the conclusions of Cohn and Swift²⁴ and others concerning the alterations in the T-wave associated with rheumatic fever.

It would seem that the serial electrocardiogram, especially with reference to the successive alterations in the T-deflection, provides a means of detecting minor damage to the myocardium which might not be recognized otherwise. This is particularly applicable to coronary artery disease in which the progression of the cardiac disability is so frequently dependent on a series of coronary occlusions. If a larger vessel is occluded the clinical manifestations are often sufficient to permit a diagnosis. It is quite likely, however, that the closure of the smaller branches plays an important rôle in the progression of the cardiac disability in this form of heart disease and is often responsible for the anginal syndrome. While further detailed clinical studies may permit a diagnosis of certain of the occlusions involving the smaller branches, the possibilities in this direction are obviously limited. Our results have shown that the ligation of the smaller arterial twigs in the dog produce characteristic alterations in the electrocardiogram, and it is believed that the same will hold for man.

CONCLUSIONS

In the present investigation the occlusion of small branches of both the right and left coronary arteries and also the opening of the pericardium without the closure of a vessel produced successive changes in the T-wave of the electrocardiogram. In each instance the alteration in the T-deflection was associated with a lesion of the myocardium. We believe that electrocardiographic changes of this character are indica-

tive of a myocardial lesion and feel that these findings may be helpful in the diagnosis of occlusion of the smaller branches of the coronary arteries in man.

We wish to express our appreciation to Dr. W. W. Herrmann of the Department of Pathology for his examination of all necropsy specimens.

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STUDIES IN OSCILLOMETRIC PRESSURE*

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INTRODUCTION

THE oscillographic study of blood pressure is not new. As far back as 1880 Marey¹ noted that blood pressure oscillations are seen to be maximal when internal diastolic blood pressure is counterbalanced by an external pressure compressing the vessel. For the measurement of these excursions various instruments were soon invented, all based upon the use of external pressure applied through an armlet connected to a measuring indicator. Readings in pulsations (oscillations) were recorded graphically or visually. Visual recording devices were used by Hill and Barnard,² Oliver,³ (using compressed air), Paehon,⁴ and Stanton,⁵ and Janeway⁶ whose instruments were based on Gumprecht's⁷ observations that the Riva Roeci sphygmomanometer could be utilized for this purpose. Graphic recording devices were employed by Gibson⁸ (with Singer's modification), Recklinghausen⁹ and Erlanger,¹⁰ and recently a Paehon apparatus† has been modified to give graphic results.

These investigators were not in agreement on the relation of maximal oscillations to either systolic, diastolic or mean pressure.‡ Thus, for example, Hill and Barnard,² also Oliver,³ fixed maximal oscillations as the mean pressure while Martin¹¹ confirmed this experimentally for an exposed artery lying on a firm flat surface but not in vivo under normal conditions. On the other hand Sahli,¹² Howell and Brush,¹³ Oliver,³ Gibson,⁸ Paehon,⁴ Recklinghausen,⁹ Erlanger,¹⁰ Janeway,⁶ confirmed Marey's contention that maximal oscillation arose at the diastolic pressure level. Tschlenoff¹⁴ expressed a view, discredited and neglected for a long time, that the maximal oscillations were associated with systolic pressure.

Recently Vaquez¹⁵ and his coworkers turned to the question anew. They quote Paehon (1921) and Gley and Gomez (1930) who, in disproving Marey's principle, established maximal oscillations as agreeing with mean pressure. The Vaquez group now maintains unequivocally that maximum oscillations do not coincide with assumed diastolic pressure; instead they consider the maximum oscillations as a visual

*From the Montefiore Hospital, Medical Service of Dr. B. S. Oppenheimer.

†Manufactured by Boultte and Co.

‡Mean pressure is not to be confused with pulse pressure. The difference between systolic and diastolic pressure is designated as pulse pressure; it represents the sudden increase in blood pressure as it distends an artery, the brachial, for instance, with each systole of the heart. Mean pressure, on the other hand, is estimated by taking the arithmetical mean of the systolic and diastolic figures. Lian (*Apparati Circulatorie*, Ed. 2, 1926) holds it more accurate to consider mean pressure as the sum of the diastolic figure and one-half the difference between the systolic and diastolic pressures.

registration at an optimum level of pressure of the largest fluctuations in intravascular pressure extant between two successive beats. According to Vaguez, this figure of the optimal level of blood pressure confusingly named "pression moyenne" (mean pressure) is an important index for studying vascular dynamics in health and disease. The French workers look upon it as a constant coefficient bearing no relation to the arithmetical mean pressure.

The purpose of our investigation was twofold: first, to note the occurrence of this phase of maximal oscillation during the cycle of pulse pressure changes, more especially placing it in its relation to diastolic, systolic, or mean pressure; second, to repeat the clinical application of oscillographic determinations, as carried out by Vaguez, in order to determine its clinical value. We used a Pachon apparatus, modified by Gallavardin to have two armlet cuffs and a simple mechanical device for releasing pressure in the armlet.

To clarify the discussion, we present Fig. 1 as a typical oscillographic record. With this as a basis we shall attempt to interpret the blood pressure excursions, correlating them with the dynamics of circulation.

PHYSIOLOGICAL CONSIDERATIONS

Fig. 1 exhibits vertical markings for the number of centimeters through which the Pachon oscillogram indicator moved at various levels of millimeter of mercury pressure, the latter being marked off on the horizontal base line. A superimposed upper curve represents a diagram of a usual radial pulse pressure graph and is seen to have its systolic point at 120 mm. of mercury, and its diastolic point at 60 mm. of mercury. A lower graph demonstrates that maximum oscillations took place at a level of 80 mm. of mercury.

The maximal oscillographic phase (MOP) is therefore 80.* If now we begin with the external pressure in the armlet cuff pumped up to 170 mm. of mercury, a level well above the systolic pressure in the brachial artery, it will be noted that no oscillations come through. This is so because the brachial vessel is completely obliterated and no pulsations are transmitted through its walls. At 150 mm. of mercury, however, the vessel has opened very slightly and the wall has begun to set up vibrations so that some oscillations are observed. The vessel continues to open, and its lumen now changes quite suddenly from a very narrow slit to a half closed shape. This abrupt transformation in contour is recorded as the systolic pressure, first, as a graphic angle, and second, by the appearance of a sound over the vessel. At this point or level of systolic pressure the external and internal systolic pressures are counterbalanced. The arterial wall, in this half closed

*This figure, i. e., 80 mm. of mercury, Vaguez would call "pression moyenne" (mean pressure). It has seemed to us less confusing to discard the term mean pressure in this connection and to look upon the figure of the level of blood pressure coincident with maximal oscillations as an index, the maximal phase or point in oscillations (MOP). This index is often a sharp peak but also not infrequently a plateau.

or flattened state of its lumen, continues to set up oscillations until a maximal phase, often a point, is reached, whereupon oscillations begin to diminish. Throughout this entire phase, it is important to realize that the lumen is half closed. With the continued drop in external compression, a point is reached where the vessel again undergoes an abrupt change, this time from a half closed to its full round circular shape. We have now reached the level of the disappearance of the systolic sound (diastolic pressure), and an angle is again registered

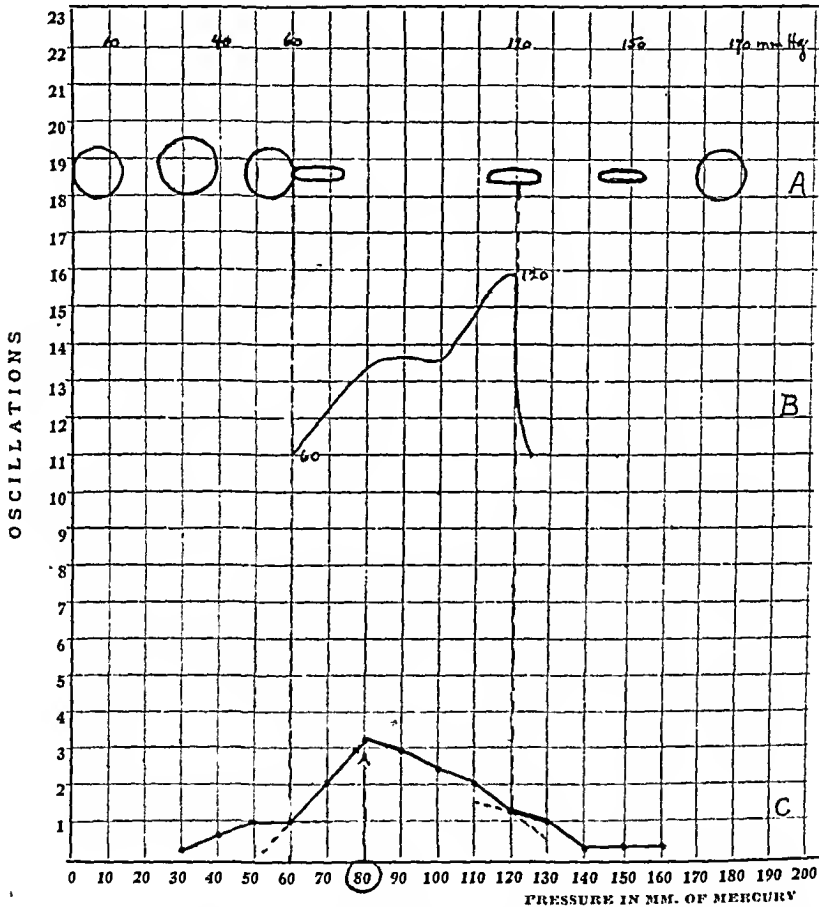


Fig. 1.—A, Cross-sections to show contour of brachial artery at various levels of mm. Hg pressure. B, Diagram of a radial artery pulse pressure graph. C, Graph of oscillometric excursions at various levels of mm. Hg pressure.

graphically. As external compression goes on falling, the vessel is seen to expand in its circular shape by its own diastolic pressure, and oscillations diminish and finally cease.

These lumen changes illustrated diagrammatically in Fig. 1 have actually been observed, and in the order and phases mentioned, by MacWilliam and Melvin,¹⁶ who claim that the phase or point of maximal oscillations does not correspond to the level of diastolic pressure. They believe that maximal oscillations take place at an optimal moment during

the half closed position of the artery lumen and that the diastolic pressure is reached only after the maximal oscillographic phase has come and gone.

The recognition that the disappearance of the systolic sound marks the level of diastolic pressure was known to Korotkoff¹⁷ but MacWilliam and Melvin definitely connected this auditory change with the abrupt visible transition in the contour of an arterial segment as seen by them through the transparent walls of an artificial compression chamber.

Although accepting and fully agreeing with auscultatory proof of the occurrence of diastolic pressure, Flack, Hill, and McQueen¹⁸ raised strong objections to the interpretations of the experiments of MacWilliam and Melvin pertaining to the changes in the lumen where maximal oscillations are concerned. They urged that no account was taken of the rôle played by the vascular tissues and channels surrounding the brachial artery, for example, in maintaining and upholding diastolic pressure, and that the artificial model of MacWilliam and Melvin represented conditions observed only when a blood vessel is isolated under laboratory conditions or compressed against a flat hard surface, as bone. To overcome these objections, Flack, Hill and McQueen¹⁹ constructed two compression chambers, one containing the blood vessel segment subjected to external pressures, the other designed to represent the resistance of the vascular tissues and venous pressure as they exist in vivo. With these chambers connected as one system they led a constantly increasing pressure into the venous channels. In a similar way they distended the artery segment with systolic pressure. They now observed in the latter a moment when the arterial wall could be flattened by external compression around the vessel, and this reading corresponded to the internal diastolic pressure in the artery. In other words, at diastolic pressure the artery was compressible, began to flatten slightly and to register pulsations which were maximal.

In the light of this apparent contradiction in interpretation concerning the relationship of diastolic pressure and maximal oscillations, we may say (1) that both groups of investigators are agreed upon the point designated as diastolic pressure according to the auscultatory method, and (2) that a study of our records of oscillographic determinations in 214 patients reveals that in human beings where no criticism can be leveled at the natural forces which cause and support diastolic pressure, we observed maximal oscillations not at the level of the disappearance of the systolic sound (diastolic pressure) but, as a rule, well above this level.*

*A point of interest is the fact that oscillations stay maximal sometimes over a plateau corresponding to a stretch extending over 20 to 30 mm. of mercury. This phase of maximal oscillations is often seen to be a peak at one particular point between the systolic and diastolic figures. In the Recklinghausen-Erlanger graphic registration, diastolic pressure is taken as that point characterized by a sudden diminution in maximum excursions. This point, however, is not always determinable because on occasions it may be impossible to obtain a sudden transition.

CLINICAL OBSERVATIONS

We studied 214 cases. Many patients were tested several times, and frequently the same patient was tested by different observers. With comparatively few discrepancies to be noted in the tables and text below and excepting the group of cases with marked myocardial damage on the basis of coronary artery disease, our observations in general are in accord with those of the Vaquez school. The exceptions are important, however, and will be discussed later.

Normal Cases.—We tested 56 normal patients, most of whom were young nurses or doctors. Twenty-seven patients ranged between eighteen and twenty-seven years of age; their MOP readings were either 80 or 90, occasionally 70 or 100; 8 patients ranged in age between thirty and thirty-eight years with MOP readings between 80 and 90; 3 patients, forty-one to forty-five years, had MOP figures of 80 to 90; 3 patients, ages fifty, fifty-one, fifty-three years respectively, had MOP

TABLE I
MISCELLANEOUS (NO HYPERTENSION)

NO.	SEX	AGE	MOP	SYSTOLIC	DIASTOLIC	
R6	M	60	80	110	75	Prostatic enlargement.
R7	F	75	100	150	90	Atherosclerosis.
R10	M	35	100	140	95	Lead poisoning.
R11	F	52	90	104	62	Anemia, parasites (intestinal).
R12	F	38	110	112	72	Cholecystitis.
R13	F	61	100	155	90	Retroperitoneal neoplasm.
R14	F	17	80	108	90	Ulcerative colitis.
R15	F	33	110	130	90	Duodenal ulcer.
R16	F	51	100	135	80	Cholecystitis, postoperative.
R17	F	59	90	124	68	Diabetes mellitus.
R8	M	53	100	130	90	Varicose veins.
R26	F	58	100	182	82	Emphysema.
R53	F	13	80	92	44	Diabetes mellitus.
3	F	72	110	112	58	Cachexia, arteriosclerosis.
6	F	60	100	128	60	Secondary anemia.
8	F	51	110	136	84	Diabetes mellitus, hepatomegaly.
17	F	42	90	140	80	Decompensated liver cirrhosis.
18	F	42	80	106	64	Decompensated liver cirrhosis.
26	F	21	90	90	58	Ulcerative colitis.
27	F	33	90	70	50	Ulcerative colitis.
123	F	67	80	124	64	Cystitis.
127	M	38	80	105	85	Bleeding duodenal ulcer.
129	F	43	110	124	84	Scleroderma.
7	M	65	80	138	84	Cholelithiasis (?) or coronary artery disease (?).
15	F	59	80	110	70	Cystitis, arthritis, coronary artery disease (?).
R65	M	22	120	92	62	Ulcerative colitis.
4	M		80	106	70	Congenital heart disease.
25	F	29	120	80	56	Patent ductus arteriosus, subacute bacterial endocarditis.
R9	M	31	100	150	82	Normal.
R2	F	58	100	150	90	Clinical angina pectoris.

figures of 90 to 100. One patient aged sixty years had an MOP reading of 80, and one aged eighty years had an MOP reading of 90.

Miscellaneous Group.—In the group of 30 patients with miscellaneous conditions (see Table I) and no hypertension, the MOP readings were normal in 23. Of the remaining 7 cases there were 5 (R12, R15, 3, 8, 129) who had a slightly elevated MOP, 110, and 2 cases (R65, 25) with the MOP at 120. In Case R65 only one reading was taken, and as there is no clinical evidence of hypertension, we are inclined to the possibility of a technical error as the cause of the high MOP. In Case 25 the MOP was verified on several different occasions and may be related to the pathological-physiological changes subsequent to the congenital defect. Case 3 was especially interesting because the patient was a little woman, aged seventy-two years, with marked emaciation and anæmia, whose weight declined to 56 pounds but whose MOP remained at 110.

TABLE II
Respiratory Conditions

No.	SEX	AGE	MOP	SYSTOLIC	DIASTOLIC	REMARKS
22	M	56	90	120	70	0 Chronic pulmonary tuberculosis, lung resection.
28	F	58	110	94	72	0 Chronic pulmonary tuberculosis, hyperthorax 4 years ago.
29	F	27	100	85	55	0 Chronic pulmonary tuberculosis.
30	F	28	90	102	84	0 Chronic pulmonary tuberculosis.
31	M	25	80	100	70	0 Chronic pulmonary tuberculosis.
126	F	43	90	106	68	0 Chronic pulmonary tuberculosis.
125	F	44	70	106	68	0 Lung resection.
124	F	36	80	118	65	0 Pleurisy effusion.
20	M	57	90	110	80	0 Pneumonia.
						0 Bronchitis, emphysema, bronchiectasis.
21	M	73	90	126	70	0 Bronchitis, emphysema, bronchiectasis.
23	M	48	100	98	73	0 Bronchitis, emphysema, bronchiectasis.
2	M	26	110	104	70	0 Bronchial asthma.
			110	123	100	0
105	M	17	90	120	70	0 Bronchial asthma.
107	M	46	100	110	70	0 Bronchial asthma.
108	M	38	100	138	80	0 Bronchial asthma.
110	F	50	100	126	70	0 Bronchial asthma.
111	F	34	90	120	85	0 Bronchial asthma.
113	M	27	100	110	76	0 Bronchial asthma.
116	F	57	90	122	70	0 Hay fever.
117	F	42	100	130	80	0 Bronchial asthma.
1	F	21	120	120	70	0 Hay fever.
			90	108	80	0 Bronchial asthma.
106	M	48	120	140	95	0
				130	90	0
109	F	33	110	125	90	0 Bronchial asthma.
112R	F	50	130	200	90	0 Bronchial asthma.
114	F	41	150	170	120	0 Myocardial damage.
115R	M	63	200	220	130	0 Bronchial asthma.
						0 Bronchial asthma.

Respiratory Conditions.—There were 26 cases in all (Table II). In 18 the MOP was normal but in 4 cases with associated hypertension the MOP was definitely elevated. In the remaining 4 cases the MOP was moderately elevated, 110 to 120. Analyzing these last 4 cases, we find that Case 28 with an MOP of 110 had had an antecedent hypertension. Case 109, with an MOP of 110, had suggestive clinical and electrocardiographic evidences of a recent coronary occlusion with a fall in blood pressure; yet the MOP remained at 110. The increased MOP in Cases 1 and 2 is difficult to explain. It varied on several different readings, only one being high in Case 1, while in Case 2 duplicate readings with slightly increased values were secured. Cases 1 and 2 received large quantities of adrenalin and ephedrine for some time, but we have no evidence that these drugs had any effect in altering the MOP readings.

Chronic Rheumatic Cardiovascular Disease.—Of 34 patients (Table III) in this group with one or more attacks of rheumatic activity, and with frank congestive failure at some time in the greatest number, only 4 had had hypertension (Cases 53, 57, 61, 74) and these 4 showed high MOP figures, i. e., from 120 to 170.

Table III also includes 20 instances of aortic insufficiency combined with mitral disease. In 2 of these (Cases R64 and 102) the MOP readings were slightly elevated despite the absence of hypertension. Subsequent oscillographic readings in R64 were always less than 100, although the original reading was 130, while in Case 102 the MOP remained at 110. We cannot explain this. In the remaining 18 patients, despite the greatly augmented pulse pressure, the diastolic pressure sometimes being at zero,* the MOP readings ranged between 80 and 90, occasionally reaching 70 or 60. This observation, previously reported by the Vaquez school, suggests that the MOP remains practically normal despite changes in pulse pressure and that the MOP and pulse pressure figures therefore cannot be identical.

A point of special interest in this connection is the comparison of the graphic, oscillographic, and the auscultatory methods for ascertaining diastolic pressure particularly in aortic insufficiency. With the auscultatory method, diastolic pressure is read at a low level, sometimes at the zero level of mercury. (Obviously diastolic pressure cannot be so low and support life.) With the oscillographic method, on the other hand, diastolic pressure is registered graphically as a terminal angle at a higher level (Fig. 1). This difference between the two methods suggests that the auscultatory method is misleading and that the systolic

*A further point of physiological and practical interest in connection with the mechanism of low diastolic pressure in aortic insufficiency relates to the explanation offered that the fall in diastolic pressure is due to regurgitant blood via the aortic orifice. This explanation is not entirely tenable because, as is well known, in cases of congenital ductus botalli with a small communicating opening where the escape of blood volume is small or negligible, diastolic pressure is liable to be quite low. Here as well as in aortic insufficiency, a loss of intravascular "head pressure" may be a responsible factor.

had hypertension despite the presence of azotemia for several years; the other (82) had a very labile blood pressure, though at times a definite diastolic hypertension was present. There are also included in this group three cases with malignant nephrosclerosis who disclosed MOP figures of 160 to 180.

Coronary Artery Disease With Myocardial Damage.—This group of

TABLE IV
HYPERTENSIVE CARDIOVASCULAR DISEASE

NO.	SEX	AGE	MOP	SYS-TOLIC	DIAS-TOLIC	
R	F	26	150	180	120	
R29	F	41	130	160	120	
R33	F	48	120	180	110	
R55	M	50	160	240	140	Friedrich's ataxia?
53	M	38	160	140	130	Chronic rheumatic cardiovascular disease, mitral lesion.
98			170	230	110	
54	F	36	120	180	100	Pluriglandular dyscrasia, diabetes mellitus, bronchitis, bronchiectasis.
57	M	53	120-130	128	72	Chronic rheumatic cardiovascular disease, myocardial damage.
58	F	62	180	280	100	Auricular fibrillation with regular ventricular rate.
60	M	49	140	160	100	Graves' disease—forme fruste.
			120	162	92	
67	F	68	130	150	75	Diabetes mellitus.
84	F	60	130	190	105	
86	F	42	120	130	90	Chronic pulmonary tuberculosis with antecedent hypertension.
88	M	47	170	190	120	
103	M	48	130	170	100	Luetic aortitis.
R54	M	60	115	110	80	Lues, antecedent hypertension.
R20	M	64	140	178	118	
R21	F	80	115	160	88	
R23	M	63	160	230	120	
R24	M	65	150	210	110	
R39	F	66	120	160	90	
R63	M	55	130	110	80	
68	F	58	170	246	94	
70	F	65	115	200	86	Diabetes mellitus.
71	F	62	120	230	110	
72	F	73	145	220	110	Arthritis, auricular fibrillation with regular ventricular rate.
80	M	59	140	188	116	
104	M	68	170	196	80	
85	M	33	160	190	110	Chronic pulmonary tuberculosis.
112	F	50	130	200	95	Bronchial asthma.
114	F	41	150	170	120	Bronchial asthma.
115	M	63	200	220	130	Bronchial asthma.
130	F	64	130	145	90	Lymphatic leucemia.
R5	F	59	160	160	96	
52	M	49	110	98	78	
				145	110	
77	M	84	120	150	48	Prostatic enlargement.
103	M	48	130	170	100	Luetic aortitis.

TABLE IV—CONTINUED
ADVANCED RENAL DISEASE

NO.	SEX	AGE	MOP	SYS- TOLIC	DIAS- TOLIC	HYPER- TENSION	
R8	F	25	170	220	165	+	Chronic glomerular nephritis, uremic.
R27	M	27	160	216	150	+	Chronic glomerular nephritis, uremic.
R49	M	50	130	168	104	+	Chronic glomerular nephritis, uremic.
R56	M	39	140	220	118	+	Chronic glomerular nephritis, uremic.
83	M	34	170	180	120	+	Chronic glomerular nephritis, uremic.
62		47	120	160	90	+	Chronic glomerular nephritis, ne- phrotic phase.
65	M	44	120	140	92	+	Chronic glomerular nephritis, ne- phrotic phase.
61	M	16	120	154	90	+	Chronic glomerular nephritis, ne- phrotic phase.
11	F	16	100	134	70	0	Chronic glomerular nephritis, ne- phrotic phase.
82	M	35	100	130	100	+	Chronic glomerular nephritis, ne- phrotic phase.
R57	M	22	180	210	140	+	Malignant sclerosis.
87	M	32	160	214	142	+	Malignant sclerosis.
R25	M	58	180	220	150	+	Malignant sclerosis.

33 patients (Table V) with coronary artery disease and in most instances showing corroborative electrocardiographic changes, is especially valuable in studying the clinical utility of the oscillometric method. Although the total number is small, these cases were carefully observed over a period of many months, a number coming to autopsy.

Coronary Artery Disease Without Hypertension (7 cases).—The MOP readings were normal in all cases. In 4 instances there had been a recent coronary artery occlusion.

Coronary Artery Disease With Hypertension (18 Cases).—In 14 instances in this group, the MOP readings were elevated. The remaining 4 cases (12, 49, 13, 10) had normal MOP readings. Of this latter group, in 3 instances (12, 13, 10) congestive failure was present at the time of the oscillometric determination.

Coronary Artery Disease With Known or Suspected Antecedent Hypertension (8 cases).—In 2 instances of known antecedent hypertension (137, 66) the MOP readings were 130 and 110 respectively. Both of these patients were in congestive failure. The remaining cases (78, 55, 5, 50, R69, 51) in which an antecedent hypertension was strongly suspected showed an elevation of the MOP readings to some degree. All but Case 51 presented evidence of congestive failure.*

At one time or another, therefore, manifestations of congestive heart failure were associated with persistent, known, or suspected antecedent

*In 2 instances (50, 137) the MOP readings were higher than the systolic blood pressure readings. This would appear to be impossible, but there is mention of this point in the literature by Flack, Hill and McQueen, and MacWilliam and Melvin, indicating that maximum oscillations may appear close to and even above the level of systolic pressure in certain pathological conditions of the arterial wall. Tschlenoff called attention to this clinically in 1905.

hypertension in the presence of normal or elevated MOP readings. These findings indicate that the maximal oscillometric phase bears no constant relationship to congestive failure.

TABLE V
CORONARY ARTERY DISEASE WITH MYOCARDIAL DAMAGE

NO.	SEX	AGE	MOP	SYSTOLIC	DIAS- TOLIC	HYPER- TENSION	
R3	M	45	90	142	78	0	Very recent coronary occlusion.
R4	M	54	80	115	70	0	
R19	F	60	100	144	98	0	
R68	M	42	80	120	80	0	
14	M	71	80	120	70	0	
19	F	70	90	140	75	0	Congestive failure.
56	F	64	110	130	90	0	Diabetes mellitus.
10	M	68	90	150	60	+	Hemiplegia.
49	F	46	100	168-120	100-70	+	Stokes-Adams syndrome, antecedent hypertension.
12	F	52	100	158-94	110-60	+	Diabetes mellitus, hemiplegia.
78	M	56	110	148-110	100-80	+	Bundle-branch block.
81	M	61	130	170-110	108-65	+	Bronchiectasis, polycythemia.
13	F	57	100	160-108	100-66	+	
R48	F	59	160	210-150	98-68	+	Diabetes mellitus.
R58	F	58	180	204-158	110-86	+	Bronchial asthma.
R60	M	55	130	210	160	+	
R59	M	65	140	190	80	+	
64	M	56	140	160	96	+	
69	F	54	160	190-114	104-70	+	
73	F	45	150	190	100	+	Bundle-branch block.
75	F	58	130	160-70	102-45	+	Diabetes mellitus.
76	F	48	190	260	140	+	
79	M	45	150	170	120	+	
57	M	53	135	164-120	120-58	+	
68	F	58	170	246	64	+	
137	M	48	130	120-86	90-64	Antecedent	Ventricular aneurysm.
66	M	64	110	114-80	85-50	Antecedent	Auricular fibrillation with regular ventricular rate.
78	M	56	115-120	138	85	Suspected	Arteriolarenal disease.
55	M	66	120-130	140-134	80-78	Suspected	Arborization block.
5	F	63	100	162	70	Suspected	
R69	M	57	100-110	138-112	78-88	Suspected	Diabetes mellitus.
51	M	59	110	138	78	Suspected	
50	M	57	100-130	128-80	92-64	Suspected	

SUMMARY

Oscillometric studies carried out on 214 patients revealed that the maximal oscillometric phase (the visual registration at an optimum level of the largest fluctuations in intravascular pressure between two successive beats) did not occur at the point of disappearance of the systolic tone (the diastolic pressure). The maximal oscillometric phase (MOP) was normal (80-100) in a group of normal cases as well as in practically all the cases in the miscellaneous and respiratory groups.

The MOP readings were definitely elevated in hypertensive cardiovascular disease.

In the instances of chronic rheumatic cardiovalvular disease, the MOP readings were within normal limits, except when associated with hypertension. In the subgroup with aortic insufficiency the MOP readings remained practically normal despite the low diastolic pressure.

In 33 cases of coronary artery disease with myocardial infarctions, 7 had normal MOP readings and had no hypertension. Among 18 instances with persistent hypertension the MOP readings were elevated in 14. In the remaining 8 cases, 2 had definite antecedent hypertension, and in 6 the clinical findings were very suggestive of antecedent hypertension. All 8 cases had elevated MOP readings.

Congestive failure appeared to have no constant relationship to the maximal oscillometric phase.

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THE COMBINED EFFECT OF EPHEDRINE AND ATROPINE ON COMPLETE HEART-BLOCK*

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THE use of ephedrine in complete heart-block was first reported by Miller⁸ (1925) in a case of complete auriculoventricular dissociation with no history of Adams-Stokes' attacks. A moderate rise of blood pressure, an increase of auricular and ventricular rate, and a change in the shape of P-waves and ventricular complexes of the electrocardiogram were noted following the administration hypodermically of 100 mg. of ephedrine. Stecher¹⁰ (1928) reported favorably the employment of ephedrine in a case of complete heart-block with syncope and convulsions due to ventricular standstill. Ephedrine was administered after barium chloride had failed to give complete relief. It was given by mouth in doses of 30 mg. three times a day for one week, followed by 20 mg. three times a day for two weeks. There was a complete absence of attacks during ephedrine therapy. The successful result in Stecher's case suggested a further study of the action of ephedrine in the presence of complete heart-block.

Two cases of complete heart-block without Adams-Stokes' syndrome were available for the study of the reaction to ephedrine and other drugs that are known to be beneficial in this condition. Studies on drugs other than ephedrine will be reported separately. The observations were made under controlled conditions. The patients were kept quiet in bed and undisturbed. Electrocardiograms were taken before and at frequent intervals after the administration by mouth of ephedrine. Blood pressure readings were made at frequent intervals and usually before the electrocardiograms, from which both auricular and ventricular rates were obtained.

Patient J. T. (Case 1) after 60 mg. of ephedrine in half an hour's time showed a rise of blood pressure from 138/54 to 142/64 mm. Hg, but practically no increase of ventricular rate which remained 40 to 41 per minute, although there was a decrease of auricular rate from 91 to 75 per minute (Table I). This slowing of auricular rate was due either to depressor nerve reflex effect from elevated blood pressure or to the stimulating effect of ephedrine on the parasympathetic nerve endings. There was no change in the ventricular complexes. Complete heart-block persisted and the difference between the P-P intervals associated with and those without ventricular contractions remained the same.

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When a larger dose (120 mg.) of ephedrine was administered, there was a further increase in the blood pressure but mainly in the systolic level, from 106/52 mm. Hg before ephedrine to 168/64 mm. forty min-

TABLE I

CASE 1. EFFECT OF A SMALL DOSE OF EPHEDRINE ON COMPLETE HEART-BLOCK. THE PATIENT RECEIVED 1.6 GM. OF DIGITALIS AUG. 17 AND 18, AFTER THAT NO MORE DIGITALIS NOR ANY OTHER DRUGS, AUG. 25 EPHEDRINE, 30 MG. BY MOUTH AT 3:20 AND 3:50 P.M.

TIME	R-R, SEC.	P-P WITH QRS, SEC.	P-P WITHOUT QRS, SEC.	P-P AVERAGE SEC.	VENT. RATE PER MIN.	AUR. RATE PER MIN.	RATIO VENT.: AUR. RATE	B. P. MM. HG	REMARKS
3:18	1.500	0.56	0.66	0.61	40	98	1:246	138/54	Before ephedrine. Ephedrine 30 mg.
3:20									
3:30	1.470	0.62	0.64	0.63	40	95	1:230	138/54	
3:40	1.480	0.68	0.76	0.72	40	83	1:205	138/58	
3:48	1.460	0.84	0.88	0.86	40	70	1:175	140/64	Ephedrine 30 mg.
3:50									
3:55	1.470	0.72	0.76	0.74	40	81	1:198	142/60	
4:05	1.445	0.71	0.73	0.72	41	83	1:202	140/60	
4:10	1.460	0.76	0.80	0.78	41	77	1:187	140/60	Complete block persists.
4:15	1.450	0.70	0.80	0.75	41	80	1:192	140/56	No change of ven- tricular complex throughout the observation.
4:25	1.440	0.72	0.80	0.76	41	79	1:189	140/60	
4:35	1.510	0.76	0.84	0.80	40	75	1:189	142/64	

TABLE II

CASE 1. EFFECT OF A LARGE DOSE OF EPHEDRINE ON COMPLETE HEART-BLOCK, AUG. 27 EPHEDRINE 60 MG. BY MOUTH AT 10:00 AND 10:55 A.M.

TIME	R-R SEC.	P-P SEC.	VENT. RATE PER MIN.	AUR. RATE PER MIN.	B. P. MM. HG	REMARKS
9:30	1.450	0.750	41	81	106/52	Before ephedrine. Fig. 1. Ephedrine 60 mg.
10:00						
10:10	1.520	0.800	39	73	106/50	
10:20	1.540	0.790	39	76	116/46	
10:30	1.490	0.710	40	84	136/58	Fig. 2. Ephedrine 60 mg. Rt. and left vent. extrasyst. Aberrant vent. complexes, occas. normal type.
10:50	1.370	0.745	43	81	154/58	
10:55						
11:00	1.340	0.640	45	94	160/60	
11:15	1.340	0.640	45	94	160/66	Fig. 3. Extrasyst. fewer. Coupled rhythm, vent. extra- syst. regularly 0.62 sec. after normal form of vent. complex.
11:25	0.900	0.640	67	94	156/56	
11:35	0.850	0.680	70	91	168/58	
11:45	0.840	0.600	71	100	168/62	
12:00	0.870	0.620	69	97	168/62	Record in sitting position Fig. 4. Note disappearance of ventricular extrasyst. and aberrant ventricular com- plexes.
12:15	0.890	0.640	68	94	168/64	
12:40	1.150	0.600	52	100	130/50	

utes after the ingestion of the drug. There was also an increase of ventricular rate from 41 to 68 and of auricular rate from 81 to 100 per minute (Table II). A marked change in the ventricular rhythm and

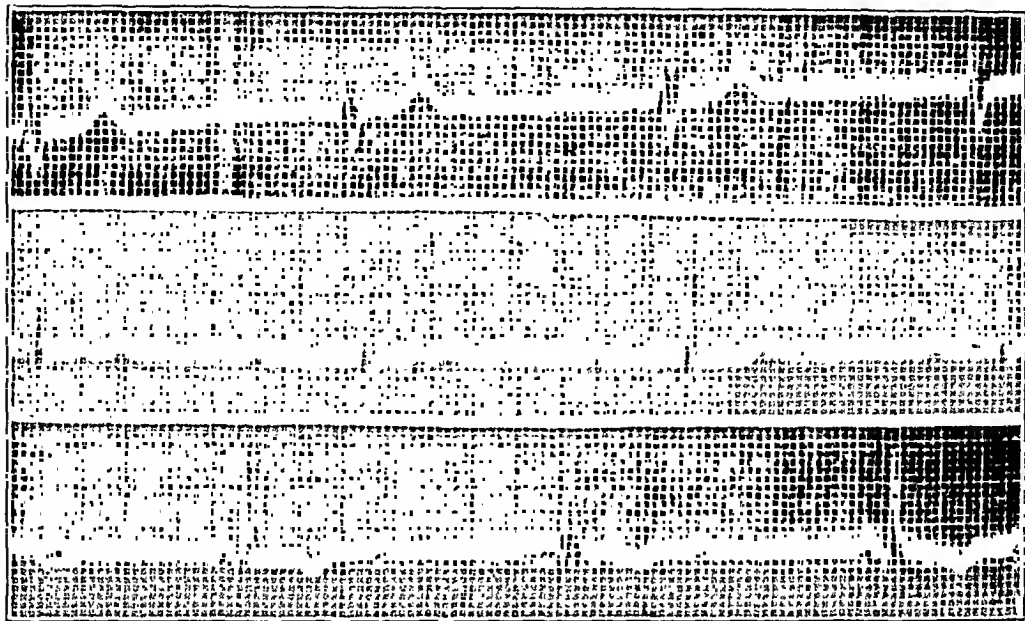


Fig. 1.—Case 1. See Table II. Electrocardiogram taken Aug. 27 at 9:30, before ephedrine. Ventricular complexes in Leads I and III are of aberrant type with S, tending to be deep. P-R intervals fairly regular, especially in Lead III, simulating two-to-one block.

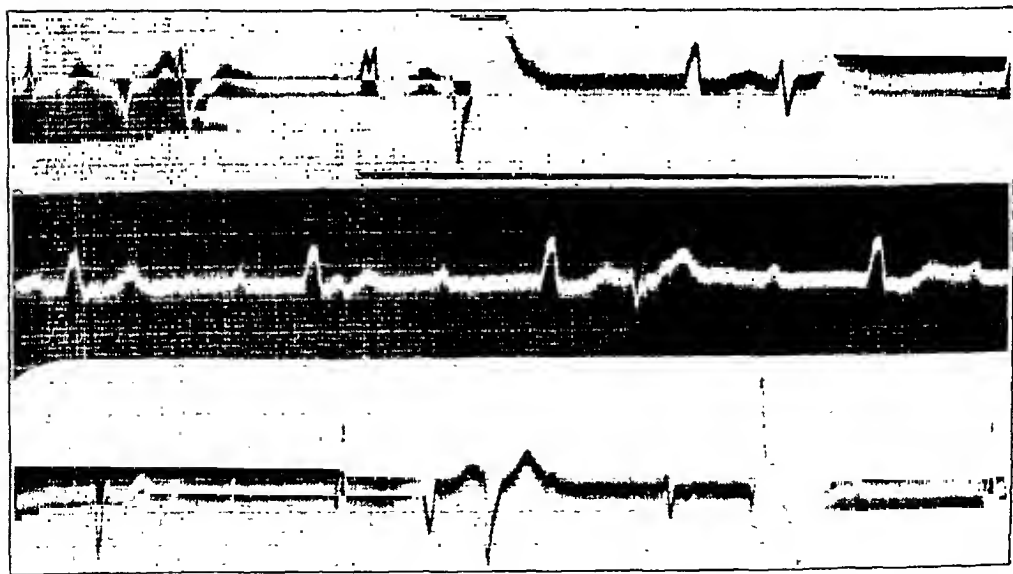


Fig. 2.—Case 2. See Table II. Aug. 27 at 10:50, fifty minutes after 60 mg. of ephedrine. Note the varied ventricular complexes extending to the form of complete bundle-branch block with intermediate types. The ventricular rhythm has become irregular and shows coupling due to right and left ventricular extrasystoles.

complexes was noted. The idioventricular rhythm became coupled or totally irregular, due to the presence of extrasystoles. The ventricular complexes of the idioventricular rhythm have the form of partial left

bundle-branch block. The extrasystoles occur at regular or irregular intervals, either alone or two or three together in succession. Their curves vary greatly, showing the forms of partial or complete bundle-branch block, possibly indicating the presence of several foci of origin. Possibly they represent reërrant excitations. (Figs. 1 to 4.) In this patient the cardiovascular reaction to ephedrine was almost like that to epinephrine in regard to the fact that increase in the dosage of ephedrine resulted in a further increase of blood pressure; also in the fact that large doses of ephedrine caused a change in the ventricular complexes and appearance of many extrasystoles, which is the usual obser-

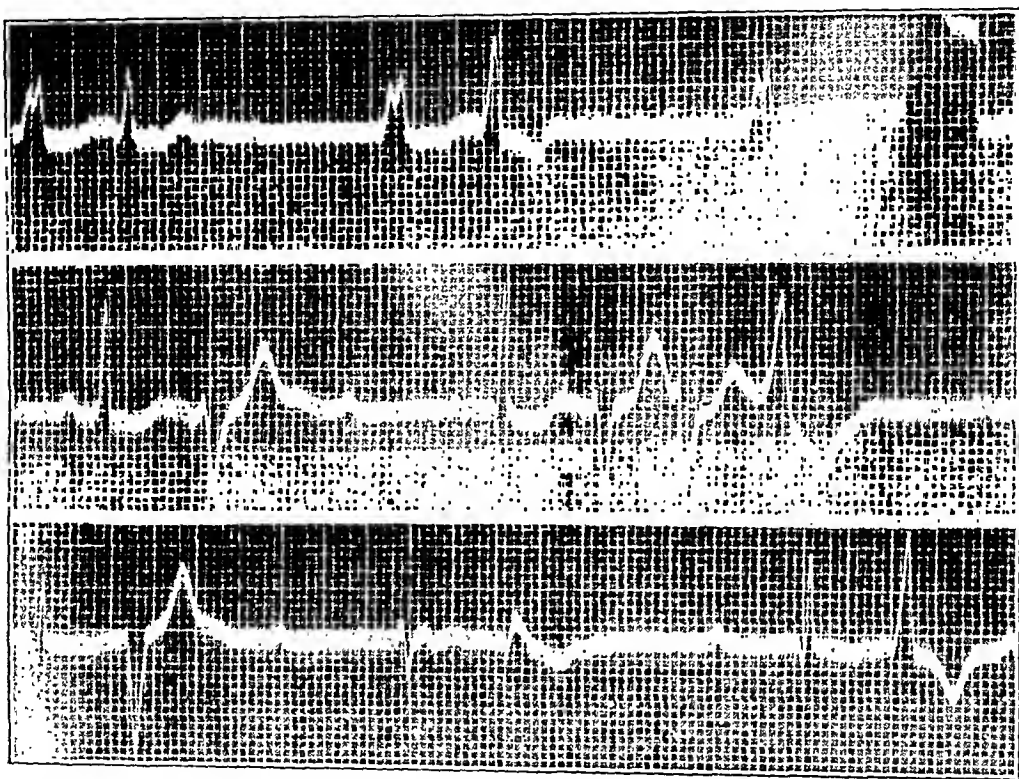


Fig. 3.—Case 2. See Table II. Aug. 27 at 11:35, twenty minutes after 120 mg. of ephedrine. Note abnormal ventricular complexes, especially in Leads I and III. The right bundle-branch type of ventricular complex present before ephedrine has changed to the left bundle-branch type. Ventricular rhythm interrupted by numerous right and left ventricular extrasystoles occurring singly or in groups.

vation after an effective dose of epinephrine, in the normal heart as well as in complete heart-block.

Patient C. K. T. (Case 2) did not show any marked pressor effect after the administration of either small or large doses of ephedrine. The results are presented in Tables III and IV. After 90 mg. of ephedrine in half an hour there was an increase of 2 ventricular beats per minute, from 37 to 39, and an increase of 15 auricular beats, from 95 to 111, and an increase of 5 mm. Hg in systolic and diastolic pressures (from 110/65 to 115/70). When the observation was repeated with a larger dose of ephedrine, 150 mg. in twenty minutes, there was no in-

crease in ventricular or auricular rate, but the same increase of 5 mm. Hg in systolic and diastolic pressures.

A marked variation in the pressor response to ephedrine such as seen in these two cases of complete heart-block is not an uncommon occurrence in individuals with normal hearts (Miller,⁸ 1925, Rowntree and

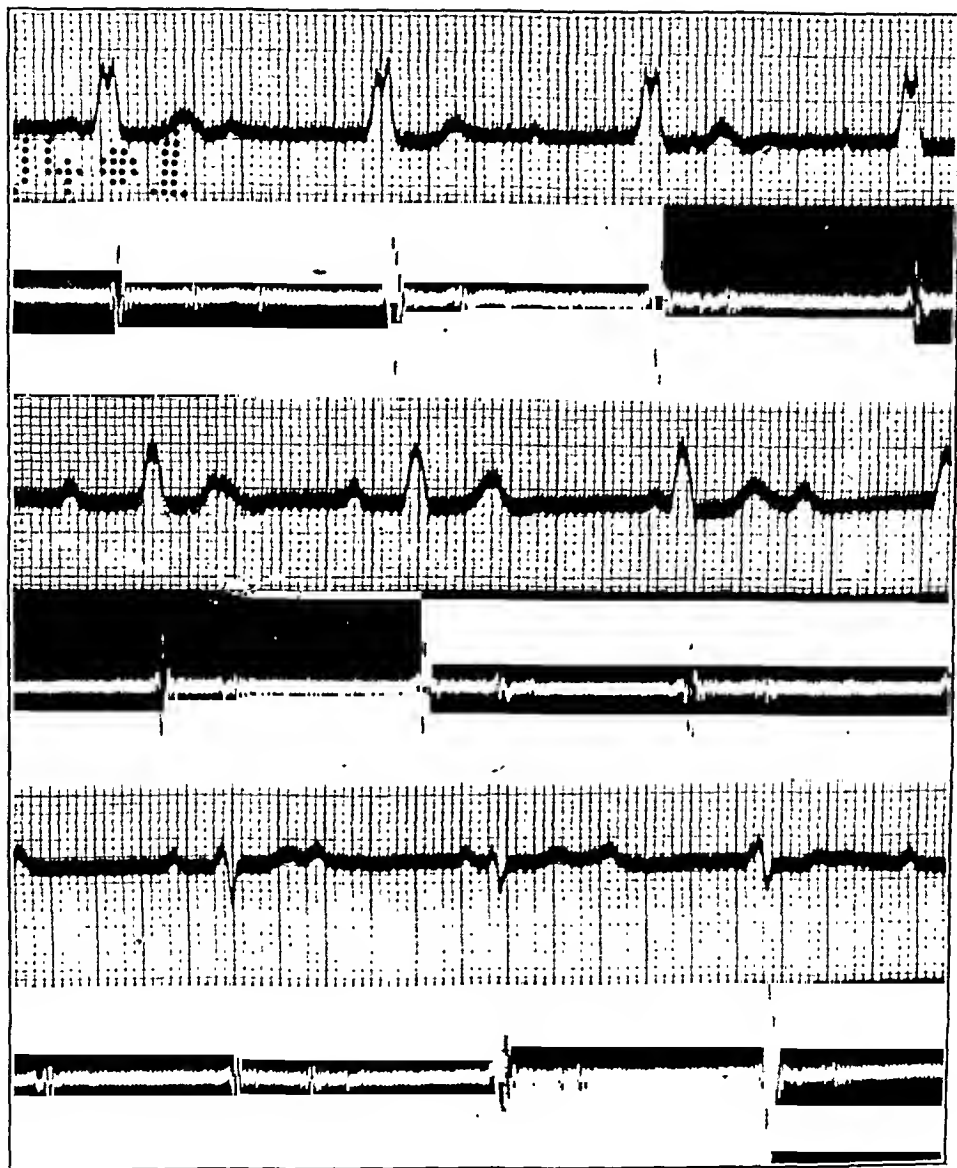


Fig. 4.—Case 2. See Table II. Aug. 27 at 12:40, in sitting position, one hour forty-five minutes after ephedrine, 120 mg. Note the disappearance of ventricular extrasystoles after slight exertion from lying to sitting position. Normal form of QRS no longer seen. The curves suggest left bundle-branch block.

Brown,⁹ 1926, etc.) and is more frequently encountered in asthmatic patients (Thomas,¹¹ 1926, Chen,¹ 1927, etc.). The explanation for the variation perhaps involves factors which are also responsible for most, if not all, of the differences in the effect upon cardiac rate. We found, however, no correlation between the rise of blood pressure and the in-

crease of auricular or ventricular rate in our cases. In Case 2 (Table III) after 90 mg. of ephedrine, the increase of auricular rate was out of proportion to the increase of blood pressure, while in Case 1 (Table I) after 60 mg., the rise of blood pressure was greater than the increase of auricular or ventricular rate. Kreitmain⁶ (1927) explained the dif-

TABLE III

CASE 2. EFFECT OF A SMALL DOSE OF EPHEDRINE ON COMPLETE HEART-BLOCK, SEPT. 14 EPHEDRINE 30 MG. BY MOUTH AT 9:12, 9:34, AND 9:54 A.M.

TIME	R-R SEC.	P-P SEC.	VENT. RATE PER MIN.	AUR. RATE PER MIN.	B. P. MM. HG	REMARKS
9:10	1.630	0.630	37	95	110/65	Before ephedrine. Ephedrine 30 mg.
9:12						
9:22	1.640	0.620	37	97	110/65	
9:32	1.650	0.620	36	97	110/65	Ephedrine 30 mg.
9:34						
9:42	1.650	0.620	36	97	115/70	
9:52	1.620	0.590	37	98	115/70	Ephedrine 30 mg.
9:54						
10:02	1.575	0.570	38	105	115/70	
10:12	1.565	0.550	38	110	115/70	Complete block persisted. No change of ventricular complex throughout the observation.
10:22	1.530	0.550	39	110	115/70	
10:32	1.515	0.540	39	111	115/70	
10:52	1.505	0.610	40	98	110/70	

TABLE IV

CASE 2. EFFECT OF A LARGE DOSE OF EPHEDRINE ON COMPLETE HEART-BLOCK, SEPT. 16 EPHEDRINE 90 MG. BY MOUTH AT 10:30 A.M. AND 60 MG. AT 10:50 A.M. A TOTAL OF 150 MG. IN TWENTY MINUTES

TIME	R-R SEC.	P-P SEC.	VENT. RATE PER MIN.	AUR. RATE PER MIN.	B. P. MM. HG	REMARKS
10:28	1.555	0.660	38	91	110/70	Before ephedrine. Ephedrine 90 mg.
10:30						
10:40	1.565	0.730	38	82	110/70	
10:48	1.570	0.600	38	78	110/70	Ephedrine 60 mg. Complete block persisted. No change of ventricular complex.
10:50						
11:00	1.580	0.755	38	80	110/75	
11:10	1.590	0.720	38	83	115/21	
11:20	1.600	0.750	37	80	115/75	
11:30	1.580	0.740	38	81	115/75	
11:50	1.575	0.760	38	79	115/75	
12:00	1.570	0.760	38	79	115/75	
12:10	1.580	0.770	38	78	115/75	

ference of pressor effect on the basis that small doses of ephedrine stimulate the sympathetic nerve endings, while large doses stimulate the parasympathetic endings.

Chen and Schmidt³ (1924) found that large doses of ephedrine depress the heart. In our cases the response to the same large dose varied. In Case 1 there was a marked pressor response and in Case 2

practically none. The actual dose may have been still "small" for Case 1, although it was "large" for Case 2, so that the absence of any appreciable pressor effect in Case 2 may be the result of depression of the heart. Another possible explanation involves limitation of the number of "receptors" in Case 2, a theory advanced by Chen and Meek² (1926). In animal experiments the depressant action of ephedrine on the heart is not antagonized by atropine according to Kreitmair⁶ (1927) and Fujii⁵ (1925). Chen and Meek² (1926) found vagotomy or

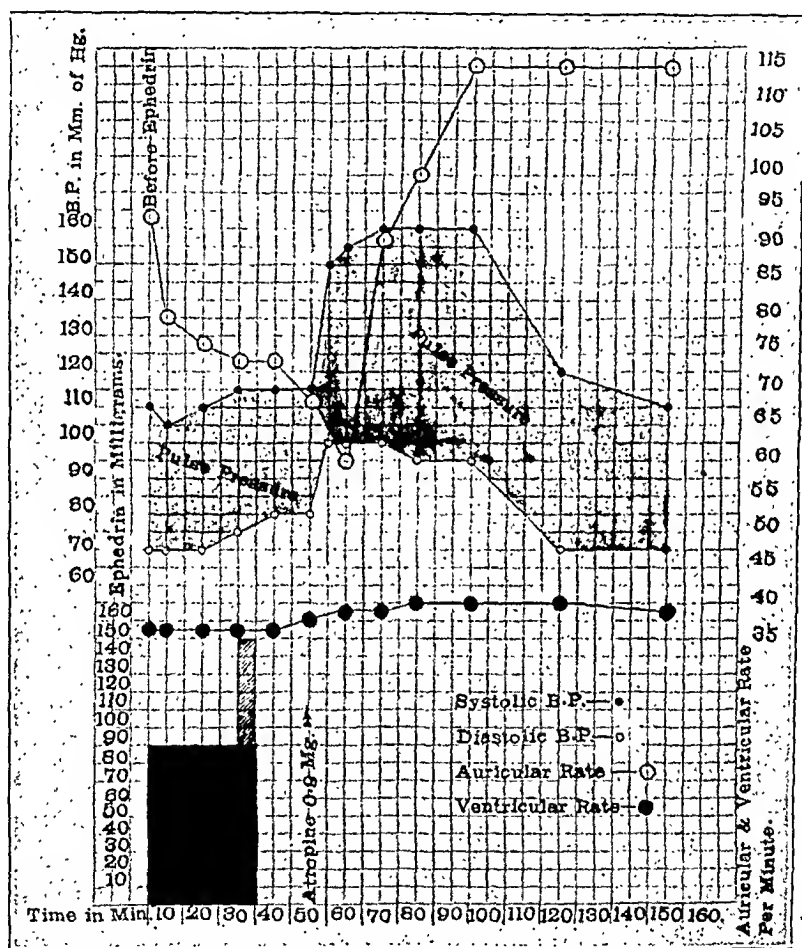


Fig. 5.—Combined effect of ephedrine and atropine one a case of complete heart-block.

atropinization did not affect the rise of blood pressure in dogs. On the other hand Mehes and Kokas⁷ (1929) believed that the depressant effect was partly removed by atropine.

To test the validity of these hypotheses in the clinical case, atropine was given in Case 2 after the patient had received ephedrine. The results are shown in Fig. 5 and Table V.

With regard to the pressor effect the results were as follows. Half an hour after the patient had received 150 mg. of ephedrine by mouth, he was given hypodermically 0.9 mg. of atropine. Two minutes after

the atropine there was a sudden rise of blood pressure from 115/80 to 150/100 mm. Hg. This elevation of blood pressure reached its maximum (160/100) in twenty minutes. The diastolic pressure began to fall before the systolic pressure. It dropped to 95 and 70 mm. Hg at thirty and seventy minutes respectively after atropine. The pressure returned to its original levels (110/70) only at the end of one hour and forty minutes, when the auricular rate was still increased. The elevation of blood pressure occurred before the increase of auricular or ventricular rate and was rather sudden. The fall was also somewhat abrupt and the

TABLE V

CASE 2. COMBINED EFFECT OF EPHEDRINE AND ATROPINE ON COMPLETE HEART-BLOCK, EPHEDRINE 90 MG. BY MOUTH AT 9:10 A.M. AND 60 MG. AT 9:32 A.M., ATROPINE 0.9 MG. HYPODERMICALLY AT 10:02 A.M.

TIME	R-R SEC.	P-P SEC.	VENT. RATE PER MIN.	AUR. RATE PER MIN.	B. P. MM. HG	REMARKS
9:08	1.585	0.640	37	94	110/70	Before ephedrine. Ephedrine 90 mg.
9:10						
9:20	1.590	0.750	37	80	105/70	
9:30	1.610	0.780	37	77	110/70	Ephedrine 60 mg.
9:32						
9:40	1.605	0.810	37	74	110/75	
9:50	1.590	0.810	37	74	115/80	Atropine 0.9 mg. hypodermi- cally.
10:00	1.565	0.870	38	69	115/80	
10:02						
10:05					150/100	Complete block persisted. No change of ventricular com- plex. No extrasystoles.
10:10	1.530	1.000	39	60	155/100	
10:20	1.515	0.680	39	94	160/100	
10:30	1.495	0.600	40	100	160/95	
10:45	1.495	0.520	40	115	160/95	
11:10	1.505	0.520	40	115	120/70	
11:45	1.510	0.520	39	115	110/70	

duration of the elevation was much shorter than that produced by ephedrine alone. Thus atropine appears to hasten and to intensify the pressor effect of ephedrine, but shortens the duration. This combined action of atropine and ephedrine is not synergy in the strict sense of the word. It suggests that atropine neutralizes the parasympathetic effect which results either from the individual's vagotony or from the stimulating action of ephedrine on parasympathetic nerves. If the lack of pressor effect after therapeutic doses of ephedrine is due either to a limited quantity of "receptors" or to depressant action of ephedrine as suggested by Chen, then atropine must increase, if not in amount at least in sensitivity, these "receptors" or it must abolish the depressant action of ephedrine on the human heart.

As to the effect on auricular and ventricular rate, after ephedrine and before atropine there was a decrease of auricular rate from 94 to 69 per minute, which persisted even ten minutes after atropine (when the

auricular rate was 60 per minute), while the ventricular rate remained constant. According to Chen and Schmidt (1924) and Chen and Meek (1926) after therapeutic doses of ephedrine pulse rate is usually slowed, occasionally accelerated. They explained the bradycardia as a reflex effect of the rise of blood pressure. In complete heart-block the vagus usually exerts little or no influence on the idioventricular rhythm but retains its control of the auricles; while the ventricles are under the influence of the sympathetic nerves. The primary slowing of auricular rate after ephedrine with practically no elevation of blood pressure in this patient would appear to be due to stimulation of the parasympathetic nerves rather than to a depressor reflex effect. The ventricles are not affected, because they are not under the influence of the vagus. About ten minutes after atropine there was a marked rise of blood pressure and a further slowing of the auricular rate (from 69 to 60 per

TABLE VI

CASE 2. EFFECT OF ATROPINE ON COMPLETE HEART-BLOCK, ATROPINE 2 MG.
HYPODERMICALLY AT 9:15 A.M.

TIME	R-R SEC.	P-P SEC.	VENT. RATE PER MIN.	AUR. RATE PER MIN.	B. P. MM. HG	REMARKS
9:10	1.680	0.860	36	70	110/70	Before atropine.
9:15						Atropine 2 mg.
9:25	1.655	0.740	36	81	100/70	
9:35	1.670	0.600	36	100	90/65	Complete block persisted.
9:55	1.720	0.610	35	98	90/65	No change of ventricular complex.
10:15	1.770	0.610	34	98	100/70	
10:45	1.795	0.650	34	92	100/70	

minute). This later auricular slowing is apparently the result of a depressor reflex effect from elevated blood pressure. At the height of the atropine effect the auricular rate increased to 115 per minute in spite of the elevated blood pressure (160/95 mm. Hg). So it seems that the depressor reflex effect on the auricular rate was abolished by atropine. There was practically no change in the ventricular rate after 150 mg. of ephedrine, but an increase of three beats at the height of the atropine effect.

As to the electrocardiographic curves there was no change in the shape either of the ventricular complexes or of the P waves. Complete heart-block persisted. No complaint came from the patient during the course of the observations. His face was noticed to be slightly flushed at the height of the reaction.

In order to exclude in this patient a possible abnormal reaction to atropine, 2 mg. were given hypodermically with no other medication. The results are presented in Table VI. At the height of the effect there was a fall of blood pressure from 110/70 to 90/60 mm. Hg. One and a

half hours later, the ventricular rate showed a slight decrease, from 36 to 33 per minute, and the auricular rate increased from 70 to 92 per minute. Evidently this patient reacted to atropine as usual.

To determine whether or not a similar action of atropine occurs in combination with pseudoephedrine, the following observations were made. Half an hour after the patient C. K. T. (Case 2) had received 150 mg. of pseudoephedrine by mouth, 0.9 mg. of atropine was administered hypodermically. The results are given in Table VII. There was no effect on the blood pressure except that the diastolic pressure increased slightly, from 65 to 70 mm. Hg for a very short time. The ventricular rate remained the same, but the auricular rate began to increase at twenty minutes after atropine and remained elevated even to

TABLE VII

CASE 2. COMBINED EFFECT OF PSEUDOEPHEDRINE AND ATROPINE ON COMPLETE HEART-BLOCK, PSEUDOEPHEDRINE 90 MG. BY MOUTH AT 9:55 AND 60 MG. AT 10:17 A.M., ATROPINE 0.9 MG. HYPODERMICALLY AT 10:49 A.M.

TIME	R-R SEC.	P-P SEC.	VENT. RATE PER MIN.	AUR. RATE PER MIN.	B. P. MM. HG	REMARKS
9:50	1.615	0.780	37	77	100/65	Before pseudoephedrine.
9:55						Pseudoephedrine 90 mg.
10:05	1.650	0.830	36	72	100/65	
10:15	1.660	0.800	36	75	100/65	
10:17						Pseudoephedrine 60 mg.
10:25	1.670	0.830	36	72	100/65	
10:35	1.680	0.930	36	65	100/65	
10:45	1.700	0.810	35	74	100/65	
10:49						Atropine 0.9 mg.
10:50	1.690	0.900	35	67	100/65	Complete block persisted.
11:00	1.655	0.840	36	71	100/65	No change of ventricular com-
11:10	1.660	0.620	36	97	100/65	plex.
11:20	1.660	0.570	36	105	100/65	
11:30	1.660	0.560	36	107	100/70	
11:50	1.690	0.620	35	97	100/70	
12:10	1.705	0.620	35	97	100/65	

one and a half hours later. Pseudoephedrine, therefore, seems not to act in combination with atropine as does ephedrine.

Unfortunately the patient J. T. (Case 1) left the hospital before there was an opportunity to study his reaction to atropine and ephedrine in combination. Three individuals with normal hearts were studied and found to have the same reaction as the patient C. K. T.

Chen and Schmidt⁴ (1930) in their recent review of ephedrine stated that the influence of atropine upon the cardiac effects of ephedrine in man apparently had not been investigated. Our results suggest that atropine either abolishes the depressant action of ephedrine on the heart in man or neutralizes the vagotony of the individual or the parasympathetic stimulation of ephedrine, thus permitting the ephed-

drine to stimulate freely the sympathetic nerve endings. The degree of pressor effect and the duration of the cardiac cycle after certain doses of ephedrine in combination with atropine are the total result of their balanced action on sympathetic and parasympathetic nerves.

SUMMARY

1. Two cases of complete heart-block responded to ephedrine quite differently. (a) With a small dose of ephedrine, Case 1 showed practically no change in auricular or ventricular rate, but a moderate elevation of blood pressure. In Case 2 there was an increase of auricular rate, but practically no change in ventricular rate or blood pressure. (b) With a large dose of ephedrine Case 1 showed an increase of auricular and ventricular rate and a marked elevation of blood pressure. The ventricular complexes varied and there were frequent ventricular extrasystoles. In Case 2 there was a decrease in auricular rate while the ventricular rate remained constant. There was practically no pressor response, and no change in the electrocardiograms.

2. In instances in which slowing of the auricles occurred without any appreciable elevation of blood pressure, the slowing may be ascribed to the stimulating effect of ephedrine on the parasympathetic nerves.

3. When an effective dose of atropine was administered to an ephedrinized patient with complete heart-block, a marked increase of auricular rate and a slight elevation of ventricular rate with a marked elevation of blood pressure and increase of pulse pressure occurred. This action of ephedrine in combination with atropine suggests that atropine neutralizes the parasympathetic effect that results either from the individual's vagotony or from the stimulating effect of ephedrine on the parasympathetic nerves.

4. Atropine hastened and intensified the pressor effect of ephedrine but shortened its duration, and abolished the depressor reflex effect of high blood pressure on the auricular rate.

5. No corresponding effect was noticed when atropine was combined with pseudoephedrine.

6. Ephedrine and ephedrine in combination with atropine did not abolish the complete block.

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A CLINICAL STUDY OF RESPIRATORY VARIATIONS IN THE FORM OF THE ELECTROCARDIOGRAM*

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VARIATIONS in the height of the various waves of the electrocardiogram, especially the QRS wave, have been universally recognized since 1910, when Einthoven first described them. Numerous articles on this subject have appeared since that time, principally by Lewis, Wenckebach, Winterberg and Gebert and Grosser. The commonly accepted explanation for this phenomenon has been that it is due to a shifting of the electrical axis as a result of changes in the position of the heart, which are mainly produced by movements of the diaphragm. Recently Condorelli¹ presented a number of clinical and experimental electrocardiograms showing marked respiratory changes, which were obviously not due to mechanical shifting of the heart's axis and yet were not conclusively proved to be due to vagal or sympathetic influence.

Although much has been written on this subject, as yet very little attention has been given to variations in the form of the electrocardiographic waves, that is, changes in a slurred or notched QRS or P-wave occurring with respiration. In a review of the literature several instances were found bearing on this particular phenomenon. Hochrein² described a case in which the electrocardiogram after an attack caused by coronary thrombosis showed a striking variation in the height and form of the R-wave synchronous with respiration, a change which previously had not been observed. In fact the majority of the tracings of the rest of his patients with myocardial infarction presented this finding. An explanation according to the idea of Hering was given, namely, that with the venous hyperemia which follows coronary thrombosis an increase in vagus tone is produced.

Also Hallermann,³ who wrote concerning the clinical significance of small ventricular excursions in the electrocardiogram, was able to show that these changes are related to disturbances in the coronary circulation. The characteristic curves published by him all show respiratory form changes, although the author did not discuss their clinical significance.

In an article on the significance of a large Q-wave in Lead III Pardee⁴ presented one case of a splintered QRS wave in Lead III, whose form changed definitely with the phase of respiration. Winternitz, in a discussion of Condorelli's¹ work, showed an electrocardiogram in which a complete shift from a left bundle-branch block in inspiration to a right bundle-branch block in expiration occurred. He believed that this

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striking change must have been due to a shifting of the electrical axis produced by diaphragmatic movements, rather than by vagal or sympathetic influence, since the administration of atropine and pressure over the carotids were without effect.

A large supply of material for the clinical study of these phenomena was offered me in the medical division of the University of Leipzig, where for the year April, 1930, to April, 1931, tracings from some 2000 patients were recorded. These consisted of the simultaneous registration of electrocardiograms and respiratory curves. The electrocardio-

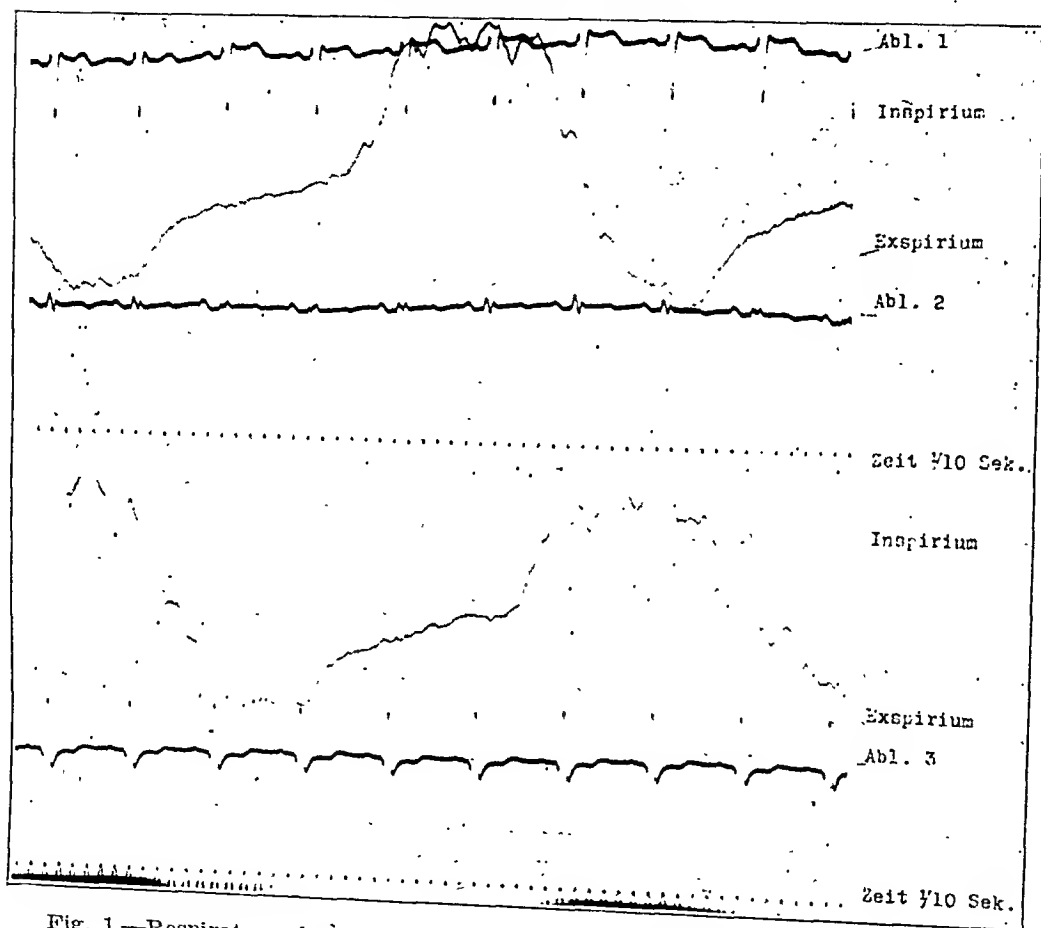


Fig. 1.—Respiratory changes in the form of the QRS wave occurring in Lead II.

grams were made with a Siemens-Halske instrument, using needle electrodes placed in the skin of the chest and left femoral region. The respiratory waves were recorded by the pneumotachograph of Hochrein, the patient reclining and breathing normally. These records are made routinely not only from all patients in the heart wards, but also from those occupying other medical stations.

Seventy-four instances of so-called form changes were found, 44 of simple variations in height with a difference of more than 2 mm., and 4 of a shifting P-wave form. The changes in form consisted of several types. The appearance and disappearance of slurring or notching of

R or S was frequently observed, the deformity coming gradually as the wave decreased in height, during expiration in the case of R_2 and S_1 , and during inspiration with R_1 and S_3 . Changes in Lead II appeared in most instances during inspiration. Exceptions to this general rule, however, occurred in all leads, most often with R_3 . Other changes consisted in the shifting of the position of a slur or notch usually simultaneously with a change in the height of the wave, although instances were found in which a difference in height was not measurable. As may be expected, these changes were found most often in Lead III, in which

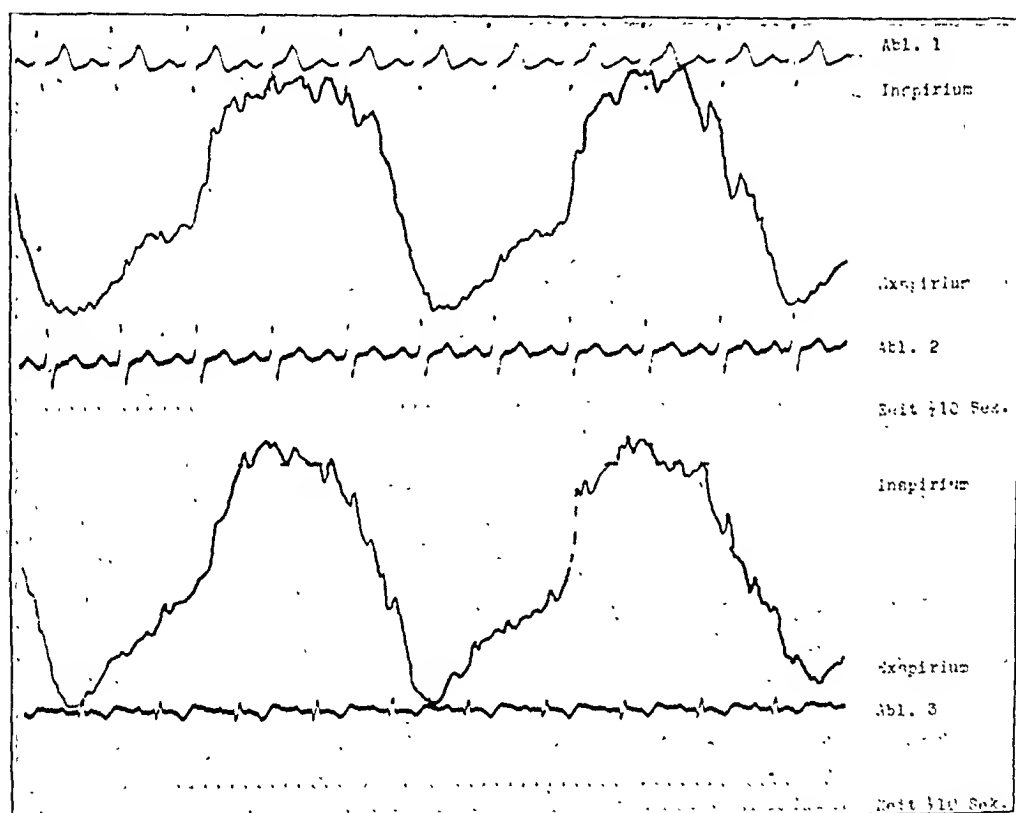


Fig. 2.—Respiratory changes in the form of the QRS wave in Lead III.

there were 48 instances. In Lead II there were 11; in Lead I, 10; in Leads I and III, 3; and in Leads II and III, 1. Changes in the form of P in relation to respiration occurred in only 4 cases. In no instance were extrasystoles found to occur consistently in one phase of respiration.

The accompanying table shows the frequency of respiratory variations in form and height of QRS in the principal types of heart disease. Of 74 patients with form changes 57, or 77 per cent, had definite clinical evidence of heart disease, while of 44 with variations in height only, 26, or 59 per cent, were clinically abnormal. Of the 57 cardiopaths in the first group, 31, or 42 per cent, of the total, were classed under coronary sclerosis, generalized arteriosclerosis or hypertension. Although these

data do not furnish the incidence of notching and slurring irrespective of respiration, it is certain that these form changes occur rather frequently in cases of heart disease especially of the degenerative type due to arteriosclerotic changes.

TABLE I

SHOWING THE INCIDENCE OF RESPIRATORY CHANGES IN QRS IN RELATION TO THE PRINCIPAL TYPES OF HEART DISEASE

DIAGNOSIS	LEAD I	LEAD II	LEAD III	LEADS I, III	LEADS II, III	TOTALS	CHANGES IN HEIGHT ONLY
Coronary sclerosis, hypertension, arteriosclerosis	5	5	19	2		31	14
Rheumatic heart disease	1	2	3	1	1	8	4
Chronic pulmonary disease	1	1	5			7	1
Hyperthyroidism	1	2	2			3	2
Aortic syphilis			2			4	0
Obesity			1			1	1
Paroxysmal tachycardia			2			2	0
Congenital lesions			1			1	1
Miscellaneous							3
Clinically normal hearts	1	2	14			17	18
Totals	9	12	49	3	1	74	44

COMMENT

The explanation of the variations in form of the QRS wave is apparently closely connected with that of variations in height, since in the great majority of instances the two occur simultaneously and with a more or less constant relationship. The older theory of shifting of the electrical axis due to the mechanical effect of diaphragmatic movements has been to a certain extent refuted by various authors. Stimulation of the sympathetic and paralyzing the vagus were demonstrated to produce similar changes by Einthoven, Rothberger and Winterberg.

Condorelli¹ found variations of this phenomenon occurring in the same individual with variations in the functional condition of the myocardium. He also observed that the depth of respiration in certain instances scarcely modified the changes in the height of R. Administration of $\frac{1}{4}$ mg. of adrenalin intravenously produced in one patient marked respiratory variations. After experimental ligation of a coronary artery in anesthetized animals he observed a striking change in all waves,

which, however, occurred not with the artificial breathing produced by intratracheal insufflation, but with the involuntary, ineffectual respiratory movements of the animal. He therefore concludes that shifting of the cardiac axis has little to do with these changes and that in all probability the extracardiac nerves can cause an increase or decrease in the potential of the heart's action current. Furthermore, in some 20 of the patients here recorded, in whom the movements of the diaphragm were abnormally limited (as observed fluoroscopically), it was observed that marked respiratory variations in form and height occurred.

Evidence against the theory of vagal and sympathetic influence is demonstrated by the failure of atropine or vagal stimulation to decrease or increase the respiratory variations. Moreover, sinus arrhythmia, which is commonly believed to be caused by changes in vagal tonus, is considered rare in cases of definite heart disease, whereas respiratory variations in the form and height of QRS waves appear frequently in these individuals.

Other factors should be considered as having a possible rôle in the production of these phenomena. It has been demonstrated experimentally by Hochrein⁵ that the blood flow in the coronary arteries varies regularly and definitely with the respiratory phase, which may be a factor in changing the potential of the action current. Variations in intrathoracic pressure affecting the amount of filling or distention of the left or right ventricle may cause a shift in the electrical axis. Chemical changes in the blood and in the tissue fluids, occurring with respiration and altering the chemical state of the myocardium, may also have an effect.

Since it is certainly far from clear what the important causative factor is in the production of these phenomena, there is need for further investigation of the problem, especially along experimental lines. Respiratory changes in the form of the electrocardiogram, though of very frequent occurrence, have heretofore not received sufficient attention in the study of this subject.

SUMMARY

In 2000 cases respiratory curves and electrocardiograms were recorded simultaneously. Respiratory changes in the form of the QRS wave were found to occur rather frequently in patients with heart disease, especially in those in the arteriosclerotic group. The cause of the respiratory changes does not appear to be due to a shifting of the axis caused by movements of the diaphragm. The influence of the vagus and sympathetic nerves, as well as changes in coronary blood flow, is briefly discussed.

The author wishes to express appreciation to Privatdozent Dr. Max Hochrein for suggesting this study and for his help and advice in the preparation of this paper.

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Department of Clinical Reports

MULTIPLE RUPTURE OF HEART BY INDIRECT TRAUMA, COMPLICATED BY MURAL THROMBOSIS AND EMBOLISM*

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SPONTANEOUS rupture of the heart is relatively rare. Krumbhaar and Crowell,¹ in 1925, made a detailed analysis of 22 of their own cases together with the 632 cases recorded in the literature since 1872. Their conclusions have been confirmed but not significantly amplified by subsequent reports of about 100 additional cases by various authors.

Most spontaneous ruptures occur through recent necrotic infarcts, some through aneurysmal dilatations of healed infarcts, and a few through abscesses, gummata, tubercles, metastatic tumors or parasitic cysts. Rarely the heart shows only the relatively benign changes of brown atrophy, fatty degeneration, and slight coronary sclerosis with atrophy and fibrosis.

The exciting cause is usually as insignificant as walking, eating or defecating. Sometimes emotional crises, violent exertion or, rarely, indirect trauma may bring about the rupture.

Nearly 80 per cent of spontaneous ruptures occur in the left ventricle, 10 per cent in the right ventricle, 6 per cent in the right auricle, and 2 per cent in the left auricle. Rupture of the septum is rare. There are several instances on record of interventricular, but only one² of interauricular, rupture. Multiple ruptures are not mentioned by Krumbhaar and Crowell but have been noted several times by others. No record of mural thrombosis at the site of the rupture with secondary pulmonary embolism has been found.

The following case is reported because it represents a unique combination of several rare aspects of spontaneous rupture of the heart: 1. The myocardium was not markedly abnormal. 2. Indirect trauma was the exciting cause. 3. The ruptures were multiple and had perforated: (a) the interauricular septum completely, (b) the interventricular septum partially, and (c) the anterior wall of the right ventricle with the exception of a transparent film of epicardium. 4. A mural thrombus had formed at the site of the interauricular defect and had given rise to a pulmonary embolus.

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Spontaneous rupture of the heart is usually found about once in 1500 autopsies. This is the fourth case in the 1500 autopsies of the University of Virginia Hospital. Two of the others have been reported previously.^{2, 3}

CASE REPORT

E. P., a colored woman about seventy-five years old, was admitted on the Orthopedic Service about twenty minutes after being struck from behind by an automobile. Her health had been excellent before the accident. For convenient reference the clinical course is presented in the form of a protocol.

PROTOCOL OF CLINICAL COURSE*

TIME	CLINICAL OBSERVATIONS	TREATMENT
10:00 A.M.	Hit by automobile.	
10:20 A.M.	Admitted to hospital. Examination disclosed: multiple fractures of ribs and legs, abrasions of left forehead, moderate degree of shock, pulse 100 and regular but for occasional extrasystoles. No dyspnea nor orthopnea. This was followed by a short period of improvement.	1000 c.c. normal saline I. V. Morphine gr. $\frac{1}{4}$. Hot water bottles.
12:20 P.M.	Pain in chest with increasing orthopnea and restlessness.	Morphine gr. $\frac{1}{6}$.
12:25 P.M.	Gasping for breath, respirations 8, pulse 110 and regular, blood pressure 70/20, pupils constricted.	Adrenalin M. XV Caffein sodio-benzoate gr. $7\frac{1}{2}$.
2:00 P.M.	Better. Respirations 16, blood pressure 110/40.	
3:00 P.M.	Semicomatose, slight pulmonary edema.	
3:30 P.M.	Better. Respirations and pulse satisfactory.	Fractures reduced and splints applied.
3:35 P.M.	Respiration and heart beat ceased suddenly, without a sigh or gasp, just after splints were applied.	

*At no time were heart murmurs heard nor were irregularities of the pulse detected (except occasional extrasystoles). Electrocardiograms were not made.

Autopsy Findings.—The body was that of an aged colored woman. External examination showed two small bruised areas on the left forehead, multiple depressed fractures of the right ribs, and compound comminuted fractures of both tibiae and fibulae.

Internal examination disclosed fractures of the fourth, fifth, sixth, and seventh right ribs near their vertebral ends. The posterior fragments were depressed and had perforated the parietal pleura giving rise to a large hematoma. These and the

fourth, fifth, and sixth left ribs were also fractured in the parasternal region but the fragments were not displaced. There was no fracture of the skull.

Brain: There were many small subarachnoid hemorrhages over the right frontal and parietal and the left parietal surfaces of the cerebrum. The fluid in the lateral ventricles was blood tinged. The vessels beneath the lining of the ventricles were congested. The choroid plexus was normal.

Lungs: There were massive adhesions between the visceral and parietal layers of the right pleura with an extensive extrapulmonary hematoma in the region corresponding to the depressed right rib fragments. An embolus occluded the middle branch of the right pulmonary artery. This lung was markedly edematous and

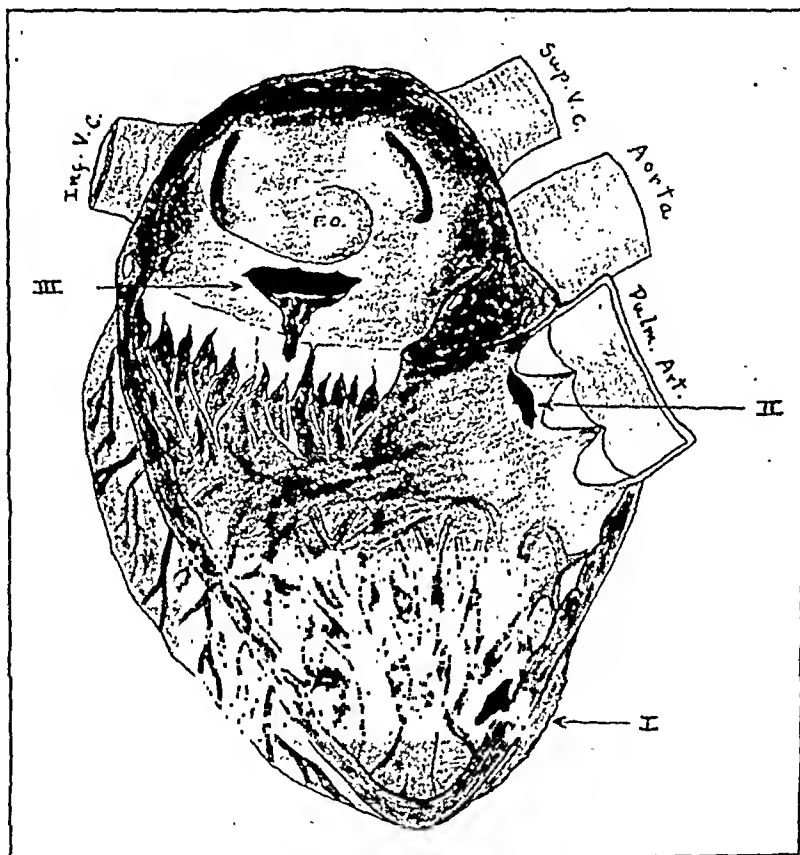


Fig. 1.—Diagrammatic sketch of right auricle and ventricle. *I*, Rupture of wall of right ventricle with subepicardial hematoma and narrow opening into ventricle. *II*, Partial rupture of interventricular septum beneath the posterior and medial cusps of the pulmonary valve. *III*, Rupture of the interauricular septum with Y-shaped thrombus attached along lower border.

slightly atelectatic. The left lung was also atelectatic and had a few pleural adhesions but was otherwise normal.

Heart: Weight 308 grams. Over the lower anterior surface above and to the right of the apex was an area of subepicardial hemorrhage, 6 by 3 cm., which communicated with a small ragged perforation of the wall of the right ventricle 3 cm. above the apex and adjacent to the septum. The ventricular aspect of this perforation was about 1 cm. in diameter. (Fig. 1, *I*.) The subepicardial opening was just large enough to admit a 1 mm. probe readily. The subepicardial hematoma contained about 2 c.c. of blood and was separated from the pericardial cavity by a transparent film of epicardium. The pericardium contained a few cubic centimeters of pale clear fluid.

Just beneath the medial and posterior cusps of the pulmonary valve (Fig. 1, II) was a small partial rupture through the endocardium and about half of the myocardium of the interventricular septum.

There was a perforation of the interauricular septum, 2.5 cm. in diameter, between the fossa orale and the A-V valves (Fig. 1, III). The edges of this perforation were smoother on the left than on the right. There was diffuse petechial extravasation of blood in the septum with corresponding subepicardial hemorrhages in the region of the right A-V junction. In the right auricle attached along the inferior border of the perforation, extending down almost to the tricuspid valve, was a Y-shaped thrombus (Fig. 1, III) which appeared to be the source of the embolus found in the middle branch of the right pulmonary artery.

The myocardium appeared normal grossly except at the sites of the ruptures. There was no evidence of infarction. The coronary arteries were slightly atheromatous but were not obstructed by thrombi, emboli, or calcium plaques. The aortic valve cusps were slightly calcified at the commissures. There was slight arteriosclerosis of the aortic arch.

Microscopic examination of the heart showed brown atrophy, fatty degeneration, small areas of atrophy and fibrosis, subepicardial and interauricular interstitial hemorrhages, and moderate intimal degeneration of the smaller coronary branches. There was no evidence of infarction.

The liver, spleen, kidneys, pancreas, adrenals, uterus, tubes, and ovaries were not significantly abnormal.

DISCUSSION

The details of the mechanism causing the heart to rupture are, of course, not known, but they furnish material for interesting, though unprofitable, speculation. There is little doubt, however, that the severe, sudden, crushing blow from behind was the exciting cause and that the myocardial degeneration, though very slight for a person seventy-five years of age, was the predisposing cause.

Death was probably due to the pulmonary embolus, with shock, contusion of the brain, and acute and chronic myocardial damage as important contributing causes. In view of the location of the ruptures the absence of murmurs is not surprising. However, the absence of disturbances of conduction is extraordinary in view of the fact that all three of the ruptures were close to the bundle of His.

SUMMARY

A unique case of rupture of the heart by indirect trauma is presented. The interesting features are:

1. Indirect trauma is a rare exciting cause.
2. The ruptures were multiple, which is rare. One was of the interventricular septum, which is also rare. One was of the anterior wall of the right ventricle, which is not uncommon. The third was of the interauricular septum. This has been reported once before.
3. A fresh thrombus formed along the edge of the interauricular rupture and gave rise to a pulmonary embolus. This has not been reported before.

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RUPTURE OF SPLENIC INFARCT IN SUBACUTE BACTERIAL ENDOCARDITIS*

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IN 1923 Blumer¹ published his monograph on subacute bacterial endocarditis. He reports that 115 infarcted spleens with 16 septic infarcts were found in 150 autopsies. He does not mention a single case of rupture of a splenic infarct. On searching the literature, we find reports of only three cases of rupture of infarcted spleen into the peritoneum. Todd² in 1919 reported a case of rupture of a septic splenic infarct. The infarct in this case was caused by a septic embolus from a gunshot wound of the leg with an infected compound fracture, and death was due to hemorrhage into the peritoneal cavity. Krokiewicz³ in 1926 reported the only case of rupture of the spleen in subacute bacterial endocarditis. He also stated that up to that time his case was unique in the literature. In this case of subacute bacterial endocarditis death was due to rupture of the splenic infarct and hemorrhage into the peritoneal cavity. Autopsy showed vegetations on the aortic valve, a septic infarct in the spleen which had ruptured into the peritoneal cavity, filling it with blood. F. J. Billings⁴ in 1928 reported a splenic abscess of unknown origin which ruptured into the peritoneal cavity, causing a generalized peritonitis and ileus. It is because of the extreme rarity of the condition and rather misleading clinical findings that we are reporting the following case.

CASE REPORT

O. L., aged seventeen years, was admitted to Minneapolis General Hospital April 11, 1931. Patient had rheumatic fever six years previously, inflammatory and migratory in type, causing him to be in bed three months. He had had similar attacks occasionally for short periods of time since. Dates and periods of these attacks were not known. There was no history of shortness of breath; but he had noticed slight weakness on extreme exertion.

During the fall of 1930, the patient had not been well, had been losing weight (18 pounds in six months), had noticed that he perspired frequently, but had been able to keep up his school work. In January, 1931, the patient ceased going to school because of his weakened condition. He continued to lose weight, noticed frequent colds, and never felt warm, although he had no definite chills. He had aches and pains in his muscles, especially in his legs.

Ten days previous to admission to the hospital patient noticed vague gastric distress, no definite pain, no nausea or vomiting, no food disturbance. Bowels functioned entirely normally. One week before admission patient developed a pain in left upper quadrant under left costal margin. At first he was not very clear as to the nature of this pain but stated later that the pain was sudden and severe in on-

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set. The pain was intensified by deep inspiration. Duration of pain one day. Patient felt fairly well after pain left.

Three days before admission to the hospital he developed a sudden severe pain located at the left costal margin, lasting about five minutes. The pain gradually became diffuse over the entire abdomen. The pain was steady, not crampy or colicky in type. At the onset of pain he had a small bowel movement, normal in color and containing no pus or blood. The same day he noticed that his abdomen was becoming distended and tense. Patient stated that he vomited four times during the forty-eight hours preceding admission to the hospital. The vomitus was brown in color and tasted foul. Patient thought that he had been passing urine more frequently the preceding few days and that it was darker in color than usual.

Physical Examination: White male, aged seventeen years, apparently anemic, fairly cooperative, in considerable pain. Head, pupils react to light, teeth carious, moderate postnasal discharge. Marked pulsation of vessels of the neck. Thyroid small. Chest, lung fields negative to percussion and auscultation. Heart boot-shaped, to percussion, markedly enlarged to left, no enlargement to the right. Retraction of interspaces with pulsation of the heart. Systolic thrill at base of the heart. No thrill felt at the apex. Systolic and diastolic murmur heard over the aortic area and well transmitted down the left border of the sternum. There was a fairly loud systolic murmur at apex of heart with faint diastolic murmur. It was felt that the diastolic murmur at the apex was a transmission from the aorta. The blood pressure was 148/48 mm. Abdomen distended, belly wall tense, no visible peristalsis, no borborygmi; tympanitic to percussion. Liver and spleen not enlarged to percussion. Spleen not palpable. Distension of abdomen interfered with this examination. There was diffuse tenderness over the entire abdomen to pressure with slight rebound tenderness localized in the right lower quadrant. There was a suggestion of a mass in the left lower quadrant. Rectal examination revealed sense of fullness in midline of pelvis with definite suggestion of a mass. Moderate tenderness to the examining finger. Extremities negative, no edema.

- Impression on admission:
1. Aortic stenosis and insufficiency.
 2. Mitral insufficiency.
 3. Subacute bacterial endocarditis.
 4. Partial intestinal obstruction,
 - a. mesenteric thrombosis or embolus,
 - b. appendicitis with ileus.

Laboratory Findings: Urine, sp. gr. 1021, no albumin, 15-20 R.B.C. and 3-4 W.B.C. per field. Leucocytosis of 27,200, differential P.M.N.'s 86 lymph. 13, mono. 1. Leucocyte count twelve hours later 20,950.

Six-foot heart plate: Total transverse diameter of chest 27.4, Ml. 12.1, Mr. 2.4. Total of heart 14.5 cm. Left ventricular type of enlargement. Diaphragm on left was poorly defined. Moderate effusion seen occupying the left pleural cavity. Lung fields clear.

Plates of the abdomen demonstrated a moderate accumulation of gas in both the large and the small bowel, the appearance suggesting an intestinal stasis, paralytic rather than on a mechanical obstructive basis. There was a suggestion of an increased density occupying the medial portion of the right iliac fossa suggesting a probable mass in this region, although this was not entirely definite.

Course: Patient was afebrile on admission. Surgical consultation was held, but it was deemed inadvisable to do a laparotomy due to the critical condition of the patient and to the fact that following rectal examination the patient passed a large amount of flatus with a watery brown stool. It was considered that the obstruction which seemed paramount on admission had been relieved by nonsurgical pro-

cedures. Temperature remained normal until one hour before death, then rapidly rose to 106° (rectal). Patient was in hospital thirty hours before death.

The autopsy was performed by Dr. N. H. Lufkin, pathologist at the Minneapolis General Hospital, one and one-half hours after death. On opening the abdomen, the peritoneal cavity was found to contain about 2000 c.c. of fibrinopurulent fluid. The omentum was matted over the bowels which were distended with gas and fluid. Peritoneal surfaces were all greatly roughened and reddened, and efforts to release the fibrinous adhesions between the bowel loops caused rupture in a number of places. The appendix was found to be normal.

The pleural cavities were free. The pericardial sac was slightly adherent to the left lung and was firmly adherent to the chest wall in the left midclavicular line and also to the right lung. The pericardial cavity was completely obliterated by old fibrous adhesions between the sac and epicardium. There was a slight bronchopneumonia in both lungs.

Heart weighed 510 grams. There was a great hypertrophy of the left ventricle with slight dilatation of this chamber. Pulmonary and tricuspid valves were normal. The aortic valve was greatly thickened and stiffened by scar tissue and calcium infiltration. The leaflets were adherent to one another at their commissures where there were great retraction and thickening. The margins were rounded and thickened by fibrous tissue, while at the bases of each there were large calcified masses, especially on the aortic surfaces. The lesion was of such an extent as to produce a severe grade of stenosis with some degree of regurgitation. The mitral valve was likewise thickened and stiffened, especially at the margins, with thickening of the chorda tendineae. There was a scarring between the two leaflets. On the margin of the mitral leaflets were found a number of small soft vegetations, some of which were rounded and pedunculated. A smear of one of these small thrombi showed the presence of numerous streptococci. The coronary arteries were normal. The myocardium was normal.

The spleen weighed 220 gm. It was firmly adherent to the diaphragm by fibrous adhesions so that considerable tearing resulted from efforts to remove it. The substance of the spleen was quite firm, but at its periphery were a number of irregular white infarcts extending to the hilus. The largest of these lesions was 3 to 4 cm. at the periphery and had undergone extensive purulent softening. Capsule over this area was extremely thin and was broken at the time of removal. Smears from its purulent content were loaded with short chained streptococci. There was a pale infarct 2 cm. in diameter in the upper pole of the left kidney.

The postmortem diagnoses were:

Old rheumatic endocarditis of mitral and aortic valves.

Recent bacterial endocarditis.

Septic infarction of spleen with rupture and streptococcus peritonitis.

Old healed pericarditis.

In summing up this case, the whole picture unfolds itself. The patient developed a rheumatic endocarditis which resulted in aortic insufficiency and stenosis and some mitral damage six years before. Then sometime during the fall and winter of 1930-1931 he developed a bacterial endocarditis. One week before admission he developed an infarct or multiple infarcts of the spleen. This caused the sudden severe pain in the left upper quadrant which was increased by deep respiration because of subdiaphragmatic inflammation. This pain then subsided and the patient felt better. Three days before admission the infarct, which

had now become an abscess, ruptured into the general peritoneal cavity, leading to a purulent peritonitis with paralytic ileus which obscured the picture and which eventually caused death. In retrospect we feel that with the story as we have it now, which we did not have on admission, we might at least have included the correct diagnosis in our diagnostic probabilities. We do not believe that surgical intervention would have offered any other end-result, first because of the severity of the peritonitis, and second because of the underlying process, namely subacute bacterial endocarditis.

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William Sydney Thayer

JUNE 23, 1864-DECEMBER 10, 1932

IT is difficult to speak of the loss sustained by American medicine in the death of Doctor Thayer without seeming to resort to extravagance and hyperbole.

The measure of his beneficent influence upon his profession is not to be reckoned merely as the sum of his accomplishments as an investigator, a teacher, a scholar, and a clinician, great as these undoubtedly were. Of greater significance perhaps than all of these sterling accomplishments was the influence of his personality upon his colleagues and upon the generations of students fortunate enough to come under his influence.

Even more than his remarkable professional attainments it was his character, his ethical standards, his generous, disinterested attitude toward every question, his eagerness to help, his capacity for warm friendship that won for him the unique position he occupied.

The loss suffered by the profession at large is fully shared by THE AMERICAN HEART JOURNAL and its editorial staff, of which he was an honored and beloved member.

Department of Reviews and Abstracts

Selected Abstracts

King, John T., and McEachern, Donald: The Nature of the Physical Signs of Bundle-Branch Block. *Am. J. M. Sc.* 183: 445, 1932.

An analysis of 50 consecutive cases of bundle-branch block showed the following physical signs: visible reduplication of the apex thrust in 42, palpable reduplication in 40; the first heart sound was split into two elements in 28, there were two separate systolic murmurs in 6 and a single first sound with a separate murmur in 8. On the basis of these signs a correct diagnosis was made prior to knowledge of the electrocardiogram in 34 of 40 attempts; the presence of bundle-branch block was suspected in 2 but was not definitely diagnosed; the diagnosis was not made in 4. There was a difference of opinion in 4 other cases. In the remaining 6 cases the presence of bundle-branch block was recognized only by electrocardiograms.

In 3 patients showing complete auriculoventricular block as well as intraventricular block, the diagnosis of both conditions was made in 2 cases from clinical signs and the signs were equally clear in the third case; signs of bundle-branch block were found, and the condition was recognized clinically in 5 or 7 patients showing both fibrillation and bundle-branch block. The latter two groups of cases show that the auricles are not concerned with the physical signs of bundle-branch block.

Presystolic gallop bears a superficial resemblance to the signs of bundle-branch block; however, clinical evidence and apex cardiograms show the two conditions to be different; presystolic gallop being truly presystolic, the signs of bundle-branch block being limited to systole and causing a division of the apex systolic plateau. Normal controls failed to show systolic reduplication.

A cinematographic film of the movement of a straw attached to the cardiac apex showed a double systolic thrust in each of 5 consecutive cases of bundle-branch block.

Mufson, Isidor: A Study of the Capillary Pressure in Nephritis and Hypertension. *Am. J. M. Sc.* 183: 632, 1932.

This investigation represents a further attempt to correlate variations of blood pressure within the minute vessels with the clinical findings in acute and chronic nephritis and in essential hypertension. Special attention has been given to the influence of capillary pressure on the development of edema. The comparison has been made between the capillary morphology found in essential hypertension and peripheral arteriolar spastic (Raynaud's) disease. From their marked difference it seems more probable that essential hypertension is due not solely to arteriolar spasm but to a generalized arterial spasm.

The frequent association of high capillary blood pressure with renal disease is indicative of a spasm response due to a severe involvement of the systemic capillary system. A relationship between the capillary pressure and the osmotic

pressure of the blood to the presence of edema has been found to exist in nephritis.

Bellet, Samuel, and Gouley, B. A.: Congenital Heart Disease With Multiple Cardiac Anomalies. *Am. J. M. Sc.* 183: 458, 1932.

Congenital heart disease in an infant is reported which presents the following unusual and rare anomalies: atresia of the aorta, hypoplasia of the left ventricle with marked thickening of its wall, hypertrophy, premature closure of foramen ovale, dilatation of right auricle and ventricle, diminutive left auricle and fibrosis of the myocardium of the left ventricle. In addition another very rare anomaly was found, the remains of the sinusoids of the embryonic heart. The incidence, theories of the origin of these anomalies and the resulting disturbances of the fetal circulation are discussed.

Samuels, Saul S.: The Incidence of Thrombo-Angiitis Obliterans in Brothers. *Am. J. M. Sc.* 183: 465, 1932.

In the examination of over 500 cases of thrombo-angiitis obliterans, the author has observed three families in which it occurred in brothers. In the first family, 3 brothers, aged thirty-four, thirty-three and twenty-nine years, showed signs of the disease. Parents of these young men were born in Austria and were apparently free from any evidence of peripheral arterial disease. Another family in which three brothers, aged forty-two, thirty-five and forty years, were affected with thrombo-angiitis obliterans was of Russian Jewish nationality; all of these were born in Russia. The third family consisted of 2 members of Austrian descent aged forty-eight and forty-three years and were born in America.

The author points out certain peculiarities of the disease, notably, its predominance in Jews, its predilection for young males, its association with cigarette smokers, its occasional occurrence in brothers with no direct evidence of inheritance.

Parkinson, John: Coronary Thrombosis. *Brit. M. J.* No. 3741, 549, 1932.

The author summarizes this presentation before the Section of Medicine at the Centenary meeting of the British Medical Association as follows: Angina pectoris is a serious disease of the heart which is manifested by pain across the chest or at the sternum, often extending into the arms, and which is due to deficient coronary circulation or imperfect blood supply. There are two main varieties, but their specific pain differs only in intensity, and their pathology has a common factor in myocardial ischemia. When the pain is brief and depends on exertion, anginal pain is known as angina of effort, and arises from ischemia due to localized arterial spasm. When an attack of anginal pain is unrelated to exertion and sufficiently prolonged, and complicated by the symptoms of infarction, it is known as coronary thrombosis, and arises from the resulting necrotic ischemia. Between these two varieties all grades of angina pectoris are encountered, in the main depending on the severity and extent of the coronary disease and the effect on the myocardium, whether the ischemia is transient (arterial spasm) or permanent (infarction). Cases of angina pectoris range from simple to severe, and present a similar pain (anginal) of varying intensity and reveal at their source a vascular identity.

Angina of effort may be initiated, complicated or terminated by coronary thrombosis. By this a simple angina (of effort) can be converted into a sort of compound or complicated angina (with shock, etc.). The correlation between anginal pain and vascular lesion is not exact, for the worst cases of angina of effort approximate to coronary thrombosis. Angina of effort is fairly inclusive of all cases of angina

pectoris excluding coronary thrombosis, cases with spontaneous attacks of pain at rest being almost invariably subject to angina on exertion.

Too much stress has been laid upon the gravity of angina pectoris. It is inseparable from a risk of sudden death, but this may be deferred for years. In attacks of coronary thrombosis and in the severer grades of angina of effort the pain is extreme and the danger is great, but milder forms are common and often run a tolerable course. There is every gradation between mild angina of effort and severe coronary thrombosis as there is every grade of coronary disease. Too much attention has been centered on the anginal death and too little on the anginal life and its management.

Bartels, Elmer C., and Smith, Harry L.: Gross Cardiac Hypertrophy in Myocardial Infarction. Am. J. M. Sc. 184: 452, 1932.

A study has been made of the weights of the heart in forty-two cases of cardiac infarction in which all other known or supposed causes of cardiac hypertrophy had been excluded. Of the forty-two cases, in 37 (88 per cent) there was definite gross cardiac hypertrophy. In five cases the weights of the hearts were not above normal. The minimal increase in weight was 18 grams (9 per cent), the maximal increase 342 grams (108 per cent), and the average increase 132 grams (42 per cent). From the data given, it would appear that cardiac infarction is a definite cause of cardiac hypertrophy.

Glover, J. Alison, and Wilson, Joyce: The End-Results of the Tonsil and Adenoid Operation in Childhood and Adolescence. Brit. M. J. No. 3740, 506, 1932.

The following summary of this paper which was read in opening a discussion of this subject, in the Section of Otolaryngology at the Centenary meeting of the British Medical Association in London, presents very important findings and conclusions from a very extensive study.

The rising flood of tonsillectomy has been shown in the immense and rapid increase in the numbers of operations annually performed and by the astonishing fact that more than half the most carefully nurtured children in this country are now subjected to it, whereas forty years ago none of their parents underwent the operation. While the incidence of tonsillitis is at least as high among the poor as among the well-to-do, the children of the latter have an incidence of tonsillectomy at least four times as high.

A review of the literature suggests that, with the single exception of diphtheria, the incidence of the ordinary infectious diseases is unaffected by tonsillectomy; that while the incidence of recurrent sore throats is perhaps somewhat diminished, that of frequent colds is unaltered, or perhaps slightly increased. The incidence of otitis and mastoid disease is the same, or perhaps slightly increased upon the tonsillectomized, while their liability to bronchitis and pneumonia is also probably slightly increased.

The evidence with regard to the prophylactic and therapeutic end-results of tonsillectomy on acute rheumatism, chorea and carditis is distressingly confusing. There is not sufficient cause for the routine removal of apparently healthy tonsils in a rheumatic or potentially rheumatic child, simply as a measure of prophylaxis against acute rheumatism. Removal should only be undertaken if there is some definite indication.

Observations have been detailed on the relative incidence of nasopharyngeal infections upon the tonsillectomized and the nontonsillectomized pupils of a school population numbering nearly 14,000. Most of these pupils were between the ages of thirteen and one-half and eighteen years and belonged to the well-to-do classes. Save for two, with a total of 1,100 pupils, all the schools were boarding schools. Rather more than half of this population was tonsillectomized. Some of the observa-

tions cover a period of seven terms, or two and one-third years, while others are confined to certain terms of epidemic prevalence.

These interim observations (so far as they have gone) give no statistical support to the theory that the removal of tonsils closes an entrance for infectious or respiratory diseases. Hardly any cases of diphtheria have occurred, so that the prophylactic value of the operation in this disease could not be assessed. In scarlet fever, otitis media and mastoid disease no significant differences were observed. In the two latter diseases the slight differences observed were in favor of the non-tonsillectomized.

These observations, based on actual attack rates in a school population, generally support the conclusions arrived at by Cunningham from a study of the histories of a similar number of somewhat older students. She found that the tonsillectomized pupils have a history of higher incidence of all illnesses and suggests that the fact that children who are often ill are those most frequently tonsillectomized may be the explanation. Comparing the proportion of the amount of illness reported before and after tonsillectomy in the same pupils, she suggests that the removal of tonsils had little influence in lessening the susceptibility to most infections.

The authors profess to hold no brief for the retention of diseased or really obstructive tonsils or adenoids, nor do they wish to cast doubt upon the high value of the operation in cases in which there is sure evidence of toxic or obstructive damage. A review of the literature and the epidemiological observations made on a highly tonsillectomized child population suggest, however, that the excellent end-results of tonsillectomy in selected cases have been statistically overweighted by indifferent end-results in cases in which the operation has been performed without sufficient indications as a more or less routine prophylactic ritual. In their opinion, a large proportion of the tonsillectomies now done in children are unnecessary, entail some risk and give little or no return.

Smith, Harry L., and Willius, Fredrick A.: Pericarditis. I. Chronic Adherent Pericarditis. *Arch. Int. Med.* 50: 171, 1932.

The records of necropsies were clinically studied, and among the 8,912 cases, 373 cases of pericarditis were found, an incidence of 4.2 per cent. One hundred and forty-four cases of adherent pericarditis were studied with particular reference to clinical and pathological correlation.

A marked predominance of the incidence in males occurred. Etiological diseases occurred in the following order: (1) rheumatic fever, (2) intrathoracic infection, (3) cardiac infarction, (4) syphilis (certainly present, probably etiologic), (5) neoplastic invasion. The weights of the hearts were determined in 105 cases. The pericardium was partially calcified in 15 cases (10.4 per cent). Associated cardiac diseases occurred in 77 cases. These in order of frequency were: (1) coronary sclerosis, (2) rheumatic heart disease with mitral stenosis, (3) hypertensive heart disease, (4) rheumatic heart disease with aortic insufficiency, and (5) aortic syphilis.

The predominant clinical syndrome was referable to the heart in 57 cases and was in no manner related to the heart in 87 cases. The latter comprised a miscellaneous group of diseases. Death from heart disease occurred in 39.5 per cent of the cases; whereas the heart was not directly concerned with death in 60.5 per cent.

Smith, Harry L., and Willius, Fredrick A.: Pericarditis. II. Calcification of Pericardium. *Arch. Int. Med.* 50: 184, 1932.

Sixteen proved cases of calcification of the pericardium are considered: in fifteen of these cases the diagnosis was established at necropsy and in one case in life. All of the sixteen patients had extensive chronic adhesive pericarditis. The diagnosis

made in life was accomplished by roentgenologic examinations. Four other clinical cases are described, but the findings were not sufficiently striking for them to be classified as proved cases. The single etiological factor that affected the largest number of cases was rheumatic infection. Tuberculosis was not present in any one of the proved cases. It was present in one of the four unproved cases. It would appear that calcification of the pericardium is a sequel of extensive chronic adhesive pericarditis and is an end-result of the same inflammatory process that produces chronic adhesive pericarditis. It is not a common condition, for it was found in only 15 of 144 cases of chronic adherent pericarditis found in this series. Recognition of deposits of calcium in the pericardium by means of roentgen rays may be an aid in making diagnosis of chronic adhesive pericarditis, which condition is extremely difficult to recognize.

Smith, Harry L., and Willius, Fredrick A.: Pericarditis. III. Pericarditis With Effusion. *Arch. Int. Med.* 50: 192, 1932.

One hundred and thirteen cases of pericarditis with effusion in which necropsy was performed at the Mayo Clinic were studied with special reference to correlation of clinical and pathological data. The cases were grouped according to the character of the effusion as follows: (1) acute purulent pericarditis, (2) fibrinous pericarditis with effusion, (3) tuberculous pericarditis and (4) noninflammatory effusion. A distinct predominance in males occurred. Infections were the etiological factors in eleven cases. Intrathoracic infectious disease occurred with greatest frequency. Infectious processes elsewhere in the body occurred in 31 cases. Only two cases were found in which infection was absent; both of these cases were examples of primary cardiac disease with congestive failure. From this study, therefore, it appears to be established that the presence of infectious intrathoracic disease offers a great chance of the pericardium being involved, and when infectious processes of the body as a whole are considered, the chance of pericarditis is still greater. Thus, the presence of infections should always focus attention on the pericardium and the result may be that purulent pericarditis or fibrinous pericarditis with effusion will be recognized more commonly. It is also of interest to observe the high incidence of pleural effusion occurring with these forms of pericarditis. Fluid was present in one or both pleural cavities in 53 cases. This observation may be applied as an accessory diagnostic sign that favors probability of the presence of pericarditis.

The cardiac weights in sixty cases in which these data were available are presented. Associated disease of the heart occurred relatively infrequently in these cases of pericarditis with effusion. There were 33 cases (29.2 per cent) in which there was associated cardiac disease, which may be compared with 53.5 per cent of cases of adherent pericarditis in which there was such associated disease. The value of so-called characteristic signs of pericardial effusion is considerable, and the presence of any such sign should be properly evaluated but their absence does not justify failure of recognition of pericarditis with effusion. Complaints predominantly referable to the cardiovascular system occurred in only 13.2 per cent of the cases. The clinical syndrome in the majority of the cases was that of sepsis. Death resulting directly and solely from heart disease occurred in only 8.8 per cent of the cases; from sepsis in 77.9 per cent, and from other causes in 13.3 per cent.

Smith, Harry L., and Willius, Fredrick A.: Pericarditis. IV. Fibrinous Pericarditis and "Soldier's Patches." *Arch. Int. Med.* 50: 410, 1932.

Sixty-two cases of fibrinous pericarditis without effusion formed a basis of this study. There are also comments on fifteen cases in which there was so-called soldier's patches or milk spots. The incidence in males was greater than that in females. Associated cardiac disease occurred in 31 cases. Although half of the

patients had associated cardiac disease, only 20 had complaints fundamentally related to the cardiovascular system. In the majority of cases in which infection occurred either spontaneously or following surgical intervention, disorders unrelated to the heart were present. The predominant clinical features in 32.2 per cent of the cases were referable to the heart; the remaining cases represented a miscellaneous group of diseases. Death from cardiac disease occurred in 32.3 per cent of the cases. In the remaining cases death was from causes unrelated to the heart. The weights of the hearts in 47 cases were available for study and are discussed.

The major subject of consideration in the etiology of fibrinous pericarditis, as one would anticipate, is an infectious process. Fibrinous pericarditis appears to be one of the simplest and most innocuous forms of pericarditis. It seems to be prodromal to more serious forms of pericarditis, namely, pericarditis with effusions in some cases, purulent pericarditis in others, and adherent pericarditis in many cases in which the patient survives the etiological disease.

Smith, Harry L., and Willis, Fredrick A.: Pericarditis. V. Terminal Pericarditis. *Arch. Int. Med.* 50: 415, 1932.

A condition classified as terminal pericarditis occurred in 40 of 373 cases of pericarditis, an incidence of 10.7 per cent. A marked predominance of the incidence in males occurred. Among the major clinical diagnoses in the cases comprising the group, those of carcinoma and nephritis predominated. Associated cardiac disease occurred in 21 cases. Death from heart disease occurred in 10 per cent of the cases. In the remaining cases, 90 per cent of the patients died of causes unrelated to the heart. Pleural fluid was present in 35.4 per cent of the cases, an accessory diagnostic sign suggesting the possibility of pericardial involvement.

Zeek, Pearl: Studies in Atherosclerosis. I. Conditions in Childhood Which Predispose to the Early Development of Arteriosclerosis. *Am. J. M. Sc.* 184: 450, 1932.

From January 1, 1931, to January 1, 1932, there were 3,072 autopsies performed on patients dying in the Cincinnati General Hospital. Of this number 1,070 were under thirty years of age; these form the basis for this investigation. The material available for the study consisted of microscopic sections averaging between 15 and 20 slides in each case and including sections from all the principal viscera; additional gross Zenker material and in many cases entire organs preserved in formalin or Kaiserling solution; clinical and pathological reports, the latter including both gross and microscopic findings. A review of this pathological material revealed definite atherosclerosis of the aorta, arteries or arterioles in 79 cases. There may have been other cases since in some of them no formalin material was available for fat stains.

It was found that rheumatic heart disease in this group was almost invariably accompanied by atheromatous changes in the aorta, pulmonary or coronary arteries. All of the four diabetic cases presented atherosclerosis of the aorta. Chronic renal lesions were found in thirty-four of the fifty-two nondiabetic, nonrheumatic cases which presented atherosclerosis and were present also in ten of the twenty-three rheumatic cases. The renal arterioles were the vessels most frequently involved in these cases. The only other pathological lesions which occurred with notable frequency in the atherosclerotic group were: focal lesions in the suprarenal medullae and hypoplasia of the malpighian corpuscles in the spleen.

Zeek, Pearl: Studies in Atherosclerosis. II. Atheroma and Its Sequelae in Rheumatic Heart Disease. *Am. J. M. Sc.* 184: 356, 1932.

Sixty-two cases of rheumatic heart disease have been analyzed with reference to the incidence of atheroma, particularly in the aorta, coronary and pulmonary ar-

teries. In twenty-eight patients under thirty-one years of age, the degree of atheroma has been compared with the duration and extent of the cardiac lesions.

Rheumatic heart disease has not been found to predispose to the early development of atheromatous lesions in the aorta, pulmonary and coronary arteries and also in the valvular and left atrial endocardium. Lipoid deposits also have been found in some cases, in the inflamed serous membranes and in certain renal tubules. Lipoid deposition has seemed to begin soon after the onset of cardiac disease and in a very general way has paralleled in degree the cardiac lesions. The atheromatous changes in many cases have been progressive, leading to calcification and when in the valvular endocardium, accentuated stenosis.

Sprague, Howard B., Burch, Hobart A., and White, Paul D.: Adherent Pericardium and Pick's Syndrome. An Autopsy Study. New England J. M. 207: 483, 1932.

A study of 1900 autopsy cases at the Massachusetts General Hospital from 1921 to 1931 in relation to pericardial adhesion is presented with special reference to Pick's disease. This was undertaken for an analysis of the possible opportunities for surgical relief of the condition as related to various etiological factors. A survey of the autopsy material at this hospital from 1893 to 1931 in regard to the incidence of Pick's disease revealed only three cases discovered at autopsy during this period. A comparison of these figures with the discharge diagnoses of the hospital cases over a period from 1923 through 1930 showed, however, that the diagnosis of chronic mediastinopericarditis had been made clinically five times. Further analysis of this clinical group showed no case proved at autopsy, but did reveal two living, in which the diagnosis appeared to be correct.

In the thirty-five-year period, during which time 6100 autopsies were studied, only six cases of adherent pericardium with a rheumatic history came to autopsy in which valvular disease was not present. None of these cases had Pick's disease.

Tuberculosis of an insidious type is the most probable cause of the constricting pericarditis of Pick. In the presence of rheumatic valvular disease and the inevitable myocardial involvement of these cases, pericardial adhesions appeared to play a secondary part in the picture of congestive failure, and in no case could it be held to be true constricting pericarditis. Adhesive pericarditis in middle or old age, even when calcified, in the absence of valvular disease is an unimportant cause of symptoms and is very rarely a contributory cause of death.

It appears unjustifiable to recommend pericardial resection following acute rheumatic pericarditis to prevent the later effects of pericardial symphysis, since valvular disease is practically always present, and the prognosis following acute rheumatic pericarditis is usually bad except for rare cases without proved valvular deformity in which no cases in this study were seen to have developed Pick's syndrome.

Edeiken, Joseph, and Wolferth, Charles C.: The Heart in Funnel Chest. Am. J. M. Sc. 184: 445, 1932.

Ten cases of moderate or severe funnel chest were studied in order to determine its effect upon the heart. There were nine males and one female. The ages ranged from seven months to sixty-nine years. The deformity was probably acquired in four cases; congenital in five cases, and unknown in one. One case was complicated by a kyphoscoliosis and pigeon breast. Clinically, the latter was the only one who showed evidence of cardiac decompensation, but it is believed this was due to the lung lesions resulting from the spinal deformity. Electrocardiograms were normal in seven uncomplicated cases. Two cases showed evidence of depressed myocardial function. Fluoroscopically the heart was flattened in the anteroposterior diameter and correspondingly enlarged in the anteroposterior view. It was displaced up-

ward and to the left and in one case appeared rotated to the right. Although the heart is displaced, electrocardiograms fail to reveal any consistent variation of the electrical axis, probably because the heart was displaced as a whole.

It is concluded that uncomplicated funnel chest does not appear to have any clearly defined effect upon the functional capacity of the heart unless the deformity is traumatic or of rapid development; the lack of symptoms can probably be explained by the slow development in the vast majority of cases. This allows for accommodation within the chest and heart.

Klotz, Oskar, and Simpson, Winifred: Spontaneous Rupture of the Aorta. *Am. J. M. Sc.* 184: 455, 1932.

An analysis is given of five cases of so-called spontaneous rupture of the aorta. A common underlying process was administered in all cases consisting of a peculiar non-inflammatory degeneration of the media affecting the muscle and elastic fibers due to a variety of factors. Similar lesions precede the development of dissecting aneurysms. A peculiar medial degeneration was found aside from spontaneous rupture or dissecting aneurysm with increasing frequency, with advancing age either as a diffuse process or in sporadic distribution through the aorta. The lesions have no relation to syphilis.

Stieglitz, Edward J., and Probst, Duane W.: Differential Arterial Tension. *Am. J. M. Sc.* 184: 336, 1932.

The arterial tension was measured in both arms in a series of six hundred individuals ranging in age from eighteen to sixty years. Whenever the difference in systolic tension was 10 mm. Hg or greater or when the diastolic difference was 5 mm. Hg or greater, an asymmetry was declared to exist. The incidence of asymmetry was slightly over 15 per cent of this group. It was found to be more common in persons with elevated arterial tension and in those with vasomotor instability. Sex was not a factor. Elevation of the systolic and diastolic tension was somewhat more frequent on the right than on the left. Arteriolar spasticity, cervical rib, aortitis, injury to an extremity with atrophy, arteriovenous aneurysm and central trophic disturbances as occur in *tuberculosis dorsalis*, are all factors to be considered in evaluating the causation of persistent asymmetry.

Adams, James M.: Some Racial Differences in Blood Pressures and Morbidity in a Group of White and Colored Workmen. *Am. J. M. Sc.* 184: 342, 1932.

A study has been made of 28,221 blood pressure readings on a group of approximately 14,000 industrial employees, between the ages of eighteen and sixty-five years, approximately one-third of whom were colored and the remainder white. All the examinations were made on apparently healthy individuals and were noted on examinations of applicants for employment (9000) and annual health examinations (5000). None were included of individuals who were sick or who consulted for medical advice. An average of three and four-fifths readings at different ages were made of the 5000 employees represented or 19,000 readings and a single reading of the 9000 applicants for employment. The period covered was from 1920 to 1930 inclusive.

From this study the following observations are apparent: The blood pressures of the colored are higher than those of the white. The pressures after forty years of age advanced more rapidly in the colored than in the white. Damage to the aortic valve occurs earlier and more frequently in the colored than in the white. Albuminuria is more often functional in the white persons and more often indicative of nephritis in the colored.

The frequency of illness was the same in both races. The recuperative powers of the colored are less than those of the white. The white race is more susceptible to respiratory and other infections, to gastrointestinal diseases, especially appendicitis and gas-

tric and duodenal ulcers, and to skin diseases, than the colored. The colored men are more susceptible to rheumatic and degenerative diseases than the whites. Venereal diseases and malaria are more prevalent among the colored, probably because of greater exposure and less prophylaxis.

Cheer, S. N., and Dieulaide, F. R.: Studies on the Electrical Systole ("Q-T" Interval) of the Heart. IV. The Effect of Digitals on Its Duration in Cardiac Failure. *J. Clin. Investigation* 11: 1241, 1932.

An electrocardiographic study was made of the action of digitalis on the R-R and Q-T intervals of patients with heart failure. A consistent decrease was found in the length of the Q-T interval in relation to the R-R interval, which was often decreased. This reduction was not always paralleled by a decrease in heart size. It is apparently an important index of the greater efficiency of the myocardium in recovery from heart failure and is interpreted as the result of a direct action of digitalis on the myocardium. The relative length of systole is a good guide to digitalis therapy. The experience of the authors leads them to believe that excessive use of digitalis is no more desirable than insufficient use, and the relative length of systole has proved a delicate guide to the danger of overdosage.

Cohn, Alfred E., and Steele, J. Murray: Studies on the Effect of the Action of Digitalis on the Output of Blood From the Heart. I. The Effect on the Output of the Dog's Heart in Heart-Lung Preparations. *J. Clin. Investigation* 11: 871, 1932.

The minute output from failing, dilated hearts in dogs in heart-lung preparations is increased when "therapeutic" doses of digitalis are administered. The effect is the opposite of that in the case of healthy hearts, normal in size. When the output increases, the pressure in the right auricle decreases. Increase in output is consistent with decrease in the diastolic volume of the heart.

If the inflow and consequently the outflow from the heart is restricted, the decrease in outflow is greater in the failing heart than in the same heart when it acts under the influence of digitalis. It appears from this test and from the discussion in the text that constriction of the hepatic veins is not a significant factor in the effect which the action of digitalis exerts on the size of the failing heart.

In estimating the value of a drug, its usefulness in therapeutics need not depend on its effect of any given function which presumably is correlated with the effect of that drug on the organism as a whole.

Book Reviews

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. Edited by Dr. Bruno Kisch. Dresden and Leipzig, 1932, Theodor Steinkopff.

The transactions of the fifth annual meeting of the German Association for the Study of the Circulation are recorded in a volume of about 350 pages which includes some forty papers. Most of these deal with the two aspects of circulatory disorders chosen for special consideration—disturbances of the arterial blood pressure and of the peripheral circulation. Each of these two topics is introduced by two important *résumé* and the whole volume bears testimony to the very substantial character of the work done by the Association. Many of the contributions are deserving of careful study.

L. A. C.

DIE ERNÄHRUNG DES HERZENS UND DIE FOLGEN IHRER STÖRUNG. By Prof. Dr. med. Luigi Condorelli, Naples. (*Ergebnisse der Kreislaufforschung*, Bd. III) 230 pages, 70 illustrations. Dresden and Leipzig, 1932, Theodor Steinkopff.

This is the third monograph in a series dealing with various experimental and clinical aspects of cardiovascular problems, published under the editorial supervision of Professor Bruno Kisch, of Köln. As the title implies, the present volume concerns itself with a discussion of the coronary circulation in health and disease. The subject matter is divided into four main parts—*anatomy, physiology, experimental pathology and human pathology*.

The first three sections, though adequately complete, constitute only about one-half of the volume, and furnish a background for the fuller consideration of the clinical features. The choice of terminology in designating the varieties of coronary disease is open to criticism. The author has chosen to divide all affections of the coronaries into two groups: A, *coronaritis*, which he calls the "Minor Coronary Syndrome"; B, *acute coronary occlusion*, designated as the "Major Coronary Syndrome." The term "*coronaritis*" suggests an inflammatory condition. Yet under this heading is included the large group of disturbances associated with atherosclerosis, as well as the less common lesions caused by syphilis, rheumatic fever, thromboangiitis obliterans, periarteritis nodosa and acute, suppurative infections. Furthermore, a sharp separation into minor and major syndromes, though perhaps helpful for discussion, is artificial, since occlusion is but one type of episode which may occur as the result of coronary disease.

Changes in the form of the electrocardiogram are given full consideration and numerous illustrative records are pictured.

An extensive bibliography is appended to each section, and due credit is given to workers in the laboratories and clinics of England, France, Germany, Austria, Italy, Scandinavia, Russia, Rumania and America. Professor Condorelli has made a critical appraisal of many of the papers cited in a manner which is possible only for one who has himself contributed to the literature in this field. The monograph represents an excellent review and should be of interest to all those who are workers in the domain of cardiology.

R. L. L.

DER CORONARKREISLAUF: PHYSIOLOGIE, PATHOLOGIE, THERAPIE. By Dr. Max Hochrein. Pp. 227, with 54 illustrations, subject and authors' index. Berlin, 1932, Julius Springer.

This monograph is an excellent summary of the entire subject of the coronary arteries, intended for the physician and investigator somewhat familiar with this field.

The literature is thoroughly reviewed, and the author shows familiarity not only with the German literature but with the foreign as well. The bibliography at the end of each section is very complete.

The author has attempted to present the subject from each of the anatomical, physiological, pathological, and clinical aspects.

The section on the anatomy is up to date. In the experimental section the author lays particular stress upon his own work. His presentation in this and the preceding section is scientific and very critical, although he shows a decided bias toward his own work. Summaries have been provided after each section so that the general reader can glean the information without the difficulty of following the detailed presentation. It is worth-while for the American reader in particular to become acquainted with the author's results and interpretations because he has come to the conclusion that Anrep's theories as to the importance of aortic blood pressure on coronary flow is not correct. According to Hochrein's results the flow is greatest during systole. Apparently he and Anrep are in accord that this is so in the intact animal as far as the superficial coronary arteries are concerned. They still differ in that Hochrein believes that the flow throughout the heart muscle is also greatest in systole, an opinion not held by Anrep. This is not the place to go into the relative merits of the two points of view. However, this study shows that there are still many factors concerning coronary blood flow which we have heretofore somewhat neglected. As a result of his studies Hochrein is inclined to believe that chemical and nervous mechanisms are as important as the mechanical. The controversies presented in this section are not at all surprising when one realizes the difficulties of evaluating the numerous variables which every worker in this field has encountered. In the section following he deals with the pharmacology of the coronary arteries, based again chiefly on the results of his own work.

The last portion of the book deals with the pathological and clinical aspects of coronary disease, in which the author brings out clearly facts accepted by all. He vacillates somewhat as to the presence of "coronary spasm" in diseased coronary vessels. He points out that mitral stenosis, by distorting the sinuses of Valsalva, may lead to narrowing of the mouth of the coronaries and he thus explains angina pectoris in such cases.

In the section on the clinical aspects of coronary disease the author's method changes from the critical scientific presentation used before to an empirical one, based on clinical judgment and personal experience. Case reports are inserted in this portion to illustrate various points. This sudden change in style of presentation has its advantages but confuses the purpose of the monograph. Summaries might have been made in this section of the monograph to aid the reader. In discussing the symptomatology of coronary disease the author presents first the general symptoms and the electrocardiogram, which latter subject is inadequately handled; he then discusses the symptom-complexes associated with coronary disease; namely, angina pectoris, cardiac asthma, and paroxysmal tachycardia. He emphasizes the significance of the personality make-up of the patient in the estimation of anginal pain. He favors the myocardial ischemia hypothesis of angina pectoris, believing, however, that very often the cause for the development of angina is a chemical or nervous action on the coronary vessels. He also suggests that nervous mechanisms may play a rôle in producing cardiac asthma. A discussion of coronary sclerosis, of syphilis of the coronary arteries and of coronary thrombosis follows. The last section of the book is devoted to the therapy of this group of cases.

In viewing the book as a whole one finds that it is apparently intended primarily for the physician especially interested in this field. Despite the appearance recently of several excellent monographs on this subject, there is a place for Hochrein's review because of the breadth of the subject matter covered in each division, and the personal experience which he has had in each of these lines. In other words, this book

is permeated by the author's own experiences; and while it sometimes has a tendency to give a one-sided picture, it serves, nevertheless, to show the interrelation of anatomy, physiology, pharmacology, and pathology in completing the clinical picture of coronary disease.

L. N. K.

LES MALADIES ORGANIQUES DU FAISCEAU DE HIS-TAWARA. LES SYNDROMES CORONAIRES—L'ENDOCARDITE SEPTALE—L'INFARCTUS SEPTAL. ÉTUDE CLINIQUE ET ANATOMIQUE. By Ivan Mahaim, Privat-docent de la Faculté de Médecine de Lausanne. Pp. 595. Paris, 1931, Masson & Cie.

In this comprehensive treatise an attempt is made exactly to evaluate all previous observations of importance relating to the disturbances of the mechanism of the heart beat produced by organic diseases of the specialized cardiac tissues discovered by His and Tawara, and a large number of original observations, splendidly illustrated with diagrams and microphotographs, are presented in detail.

The first part of the book is devoted to the physiology, anatomy, and histology of the His-Tawara system and to methods of examining its structure and studying its functional integrity. The blood supply receives special attention, and a résumé of the essentials of clinical electrocardiography is included.

The second part is concerned with the correlation of the microscopic lesions found post mortem and the changes in the mechanism of the heart beat observed during life. The first three chapters of this section deal with destructive lesions resulting in conduction defects. After reviewing all of the cases that have been published as demonstrating a relation or lack of relation between atrioventricular heart-block and lesions of the conducting system and describing four of his own cases of complete block in which a complete microscopic examination of this system was carried out, Mahaim draws the following conclusions:

When the continuity of the His-bundle is completely destroyed permanent and complete atrioventricular dissociation is invariably present.

Permanent complete heart-block is always organic in origin.

Complete atrioventricular dissociation is often due to lesions that involve both branches of the bundle rather than the main stem or node of Tawara.

There is no necessary relation between the apparent degree of a partial lesion and the degree of dissociation produced by it. An almost complete lesion may be associated with normal conduction or with an insignificant conduction defect.

Nineteen cases of supposed complete bundle-branch block in which the branches of the bundle were examined histologically are reviewed. Only three of these (the two cases published by Eppinger and Stoerk and one reported by Kauf) are regarded as entirely satisfactory from the standpoint of demonstrating that the lesions discovered were responsible for the electrocardiographic abnormalities observed. Mahaim gives a detailed description of eight additional cases studied by himself. In six of these the continuity of the right branch of the bundle was completely interrupted. The electrocardiograms are reproduced, and all show some degree of left axis deviation. The QRS-intervals range from 0.09 to 0.16 second; the measurements given are 0.11, 0.10, 0.10, 0.09, 0.16, and 0.09 second respectively. With one exception none of these electrocardiograms could be regarded as depicting complete branch block if the criteria in common use were adhered to. In a seventh case both bundle-branches were completely transected by destructive lesions. The electrocardiogram shows auricular fibrillation with a ventricular arrhythmia of the type usually associated with this condition. The ventricular complexes are of small amplitude, and the QRS-interval is given as 0.12 second. Ventricular extrasystoles frequently occurred. According to Mahaim's interpretation complete atrioventricular dissociation is present with an irregular idioventricular rhythm arising in the left bundle branch below the lesion. In an eighth case the left bundle branch was almost completely interrupted. The electrocardiogram shows right axis deviation with a QRS-

interval of 0.10 second. In all of these cases the lesions were multiple, and both branches were more or less involved.

With regard to the electrocardiographic abnormalities produced by complete interruption of the continuity of the right bundle branch, Mahaim concludes that left axis deviation is invariably present; that the QRS-interval is often not prolonged beyond 0.09 or 0.10 second; that the ventricular deflections are frequently of small amplitude, particularly when subdivisions of the left branch are also involved, and that the abnormalities of the T-deflections are proportional to those of the QRS-deflections. He apparently believes that a very large percentage of the curves at present attributed to preponderant hypertrophy of the left ventricle are due to right branch block, complete or incomplete.

Destructive lesions of the right bundle branch, which receives its blood supply by way of the anterior descending branch of the left coronary artery, are almost invariably vascular in origin and are usually associated with lesions of the anterior subdivisions of the left branch, which are nourished by the same artery. Complete lesions of the left branch are almost never vascular in origin, but are usually due to the extension of a valvulitis, involving the aortic or mitral valve, to the septum. The main stem of the bundle is likely to be involved at the same time so that left branch block without complete atrioventricular dissociation is rare.

Four chapters are devoted to lesions of the specialized tissues associated with hyperexcitation, i. e., with attacks of ectopic tachycardia arising in the affected region. Ischemic, inflammatory, or degenerative lesions may act in this way. When the tachycardia is due to lesions of the bundle branches, the ventricular complexes may be polymorphous, or alternation in the form of these complexes may occur. Mahaim apparently believes that digitalis produces ventricular tachycardia of this type only in cases in which organic lesions of the conducting system are present.

The last part of the book deals with the relation of lesions of the conducting system to coronary, myocardial and valvular disease and to congenital anomalies of the heart, particularly defects of the ventricular septum. Mahaim believes that obliterative vascular lesions involving the anterior descending branch of the left coronary artery produce a characteristic syndrome; insufficiency of the left ventricle, enlargement and deformity of the left ventricle, and right branch block. The deformity of the left ventricle, due to aneurysm of the apex and adjacent portions of the wall, may be recognized by roentgen-ray examination.

On the whole this treatise, which ends with a list of over one thousand articles bearing on the subjects discussed, should prove a valuable work of reference. It may be noted, however, that many of the opinions expressed therein are at variance with recent observations that have appeared since it came off the press. If, as now seems practically certain, classical views regarding the electrocardiographic identification of right and left ventricular extrasystoles and right and left branch block must be revised, many of Mahaim's observations become inexplicable and many of his views untenable.

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GALLOP RHYTHM AND THE PHYSIOLOGICAL THIRD HEART SOUND

I. CHARACTERISTICS OF THE SOUNDS, CLASSIFICATION, COMPARATIVE INCIDENCE OF THE VARIOUS TYPES AND DIFFERENTIAL DIAGNOSIS*

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THERE is considerable disagreement in the literature concerning the characteristics and significance of gallop rhythm and its relation to the physiological third heart sound. The differences of opinion are clearly stated in Holt's¹ excellent review of the subject. During the past four years we have been collecting clinical material and applying various laboratory methods in an effort to obtain data bearing on these problems.

One of the difficulties encountered early in the work was that of fitting certain cases into proper categories. There is no doubt as to the usefulness of Potain's² classification based on time relations, in so far as it applies to protodiastolic and presystolic gallop. The relationships of the type of gallop which he called mesodiastolic, however, have not been clearly determined. Mesodiastolic gallop, according to Potain, is either presystolic or protodiastolic gallop which happens to occupy a position in mid-diastole because of tachycardia. This view was based on auscultatory studies and the position of diastolic filling waves in apex cardiograms, methods which must be recognized as inadequate. Thus the question as to whether or not mesodiastolic gallop deserves recognition as a distinct entity, has up to the present time remained unanswered.

From the above considerations it seemed that the classification of gallop rhythm was not completely satisfactory and that the subject required further investigation. We have therefore attempted to clarify the situation, and in this report offer what we believe to be a theoretically sound

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and practical classification including both gallop rhythm and physiological third heart sounds.*

MATERIAL AND METHODS

The observations on gallop rhythm and the physiological third heart sound constitute part of a more comprehensive study including the opening snap of mitral stenosis,³ reduplication of first and second heart sounds and other sounds (exclusive of murmurs) heard during the cardiac cycle. The material was obtained from all available sources, chiefly hospital ward and outpatient departments. Private patients and University students referred to the Section for examination were also utilized. Most of the observations on which this report is based were made in 70 cases, of which 60 were classified as having gallop rhythm, and 10, physiological third heart sounds. For inclusion in the group, it was required not only that the gallop or third sound be heard on auscultation, but also that it be clearly recorded by sound registration apparatus. All patients were subjected to fairly complete physical examination, and nearly all those with gallop rhythm were under observation for periods varying from several weeks to four years.

In all cases electrocardiograms were recorded simultaneously with the sound registration. Especial care was taken to avoid parallax, so that the time relations and positions in the heart cycle of the various sound waves could be determined. The sound registration methods used have been mentioned previously.³

THE DIFFERENTIATION BETWEEN GALLOP AND THE PHYSIOLOGICAL THIRD HEART SOUNDS

Thayer⁴ and more recently Gubergritz⁵ have emphasized the similarity of physiological third heart sounds and gallop sounds. Gubergritz believes, however, that there are certain differences in quality and intensity of the sounds. We have observed no essential differences in quality, location, time relations, or the influence of posture or various maneuvers to alter the sounds. The only criterion available for differentiation, aside from the fact that physiological third heart sounds become increasingly rare with advancing age, is the status of cardiac function. When the cardiac function is obviously altered from the normal, the sounds are arbitrarily classed as gallop sounds. If no abnormality is detected, the sounds are regarded as physiological third heart sounds.

It would be more satisfactory if other criteria besides the status of cardiac function were available in youthful patients for deciding whether a third sound should be designated as a physiological third heart sound or

*The so-called systolic gallop rhythm is not considered in this paper. These systolic sounds must have a fundamentally different mechanism of production from the gallop sounds which occur during diastole. They are rarely heard, have apparently little clinical importance, and in order to avoid confusion should be given a name which does not include the term "gallop."

as part of gallop rhythm. The differentiation has considerable practical utility. The rather loud third sounds sometimes heard during hyperthyroidism, anemia, the active stages of rheumatic fever and occasionally in other infections, are clearly associated with these pathological states. They usually disappear, or at least become much less distinct, upon the subsidence of these conditions. Thus, they are a manifestation of disease and according to our present nomenclature should be called gallop rhythm.*

Physiological third heart sounds can be elicited in a considerable percentage of children and young adults provided the methods devised by Thayer⁴ are employed. If already present they can sometimes be greatly intensified by these methods. Occasionally, however, instead of becoming louder the sounds vanish in left lateral decubitus, which is ordinarily the position most conducive to their appearance. The group of 10 cases included in the present study was specially selected for sound registration since all had third heart sounds easily heard in either dorsal or left lateral decubitus.

CHARACTERISTICS OF THE SOUND

a. Quality and Loudness.—Third sounds (both gallop and physiological third sounds) are almost invariably dull and low-pitched. The phenomenon has frequently been described as a "thud" or "shock" which can sometimes be more distinctly palpated than heard.† The low vibration frequency of the main oscillations in sound tracings of physiological third sounds has been pointed out by Bridgeman.⁶ Gallop sounds have a similarly low vibration frequency. The sounds are characteristically short in duration. When, however, two gallop sounds occur during the same heart cycle (protodiastolic and presystolic) and the heart rate is such as to bring them close together, the resulting sound may be reduplicated, prolonged or may actually resemble a short murmur. The loudness of the sounds varies widely. As a rule, they are much less audible than the first or second sounds and may escape detection unless the examiner has them in mind. Occasionally, however, the third sound may be louder than either the first or second sound or both. (Fig. 1 and Fig. 8, lower strip.)

Respiratory variations in the loudness of gallop or physiological third sounds are present in many cases and tend to be much greater than respiratory variations in either the first or second sound. In some cases the sound may be quite loud near the end of expiration and either faint or absent when the lungs are filled. (Fig. 2.) However, independently of respiration, there is remarkable variability and inconstancy of gallop, a char-

*There is always the possibility, indeed the probability, in young patients that a physiological third heart sound might have been present before the development of a morbid state. Such a sound may be accentuated merely by the tachycardia accompanying the disease. Before designating the sound as gallop, it should be demonstrated that its presence, or at least, its accentuation was due to the disease and not merely to tachycardia.

†The sensation obtained on palpation is probably derived chiefly from the large single wave of ventricular filling.

acteristic which must impress every one who studies these sounds. This phenomenon is well exemplified in a large group of cases excluded from the present study because of the fact that, although gallop sounds had been present at the original examination, they were either no longer present or so faint that they could not be recorded satisfactorily when the patients were sent to the laboratory.

b. Location.—In the great majority of cases the gallop sound is heard best in the neighborhood of the apex impulse. (Fig. 3.) When the sound is faint, it may be sharply limited to this position. When it is loud, however, it may be heard over a considerable area. Occasionally gallop sounds are heard best over or just to the left of the lower end of the sternum.

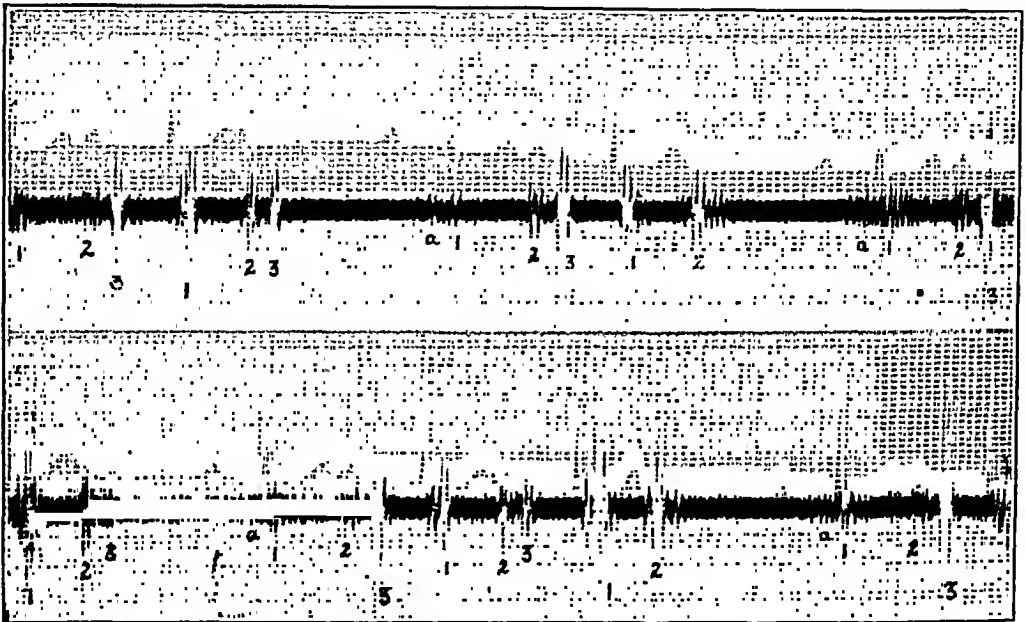


Fig. 1.—Incomplete heart-block and gallop rhythm occurring in a boy fourteen years old following an attack of streptococcic sore throat. (Continuous tracing.) Marked variation in amplitude of vibrations of gallop sounds. The small vibrations marked "a" are due to auricular activity alone. These were not audible. The protodiastolic vibrations in beats 1 and 4 of the lower tracing are little if any influenced by auricular activity. In the last beat of the upper strip, and the second and fifth beats of the lower strip, auricular contraction falls at a time favorable for the production of very loud gallop sounds which not only have an amplitude far greater than either the first or second heart sound but on auscultation were found to be much louder. The variations in intensity of the first heart sound are due to varying A-V relations.¹⁰

Among our cases the sound was heard best over the apical area in 53, near the lower edge of the sternum in 3; while in 2 cases it was sometimes louder at the apex, and sometimes louder near the lower edge of the sternum.

In all individuals with physiological third heart sounds whom we have studied, the third sound was heard best in the region of the apex impulse. As in gallop, when the sound is loud, it may be well heard over a considerable area.

c. Time Relations.—In the cases of third heart sound studied by Bridgeman,⁶ the interval between the beginning of the second and third sounds ranged from 0.13 to 0.18 second. Bridgeman noted that small presystolic

vibrations were also present in the sound records of 11 out of 16 cases. He states that these "sounds" are "generally" below the limit of human audibility. Battaerd,⁷ and Michaud and Fleisch⁸ have also recorded these apparently subsonic presystolic vibrations. Although these small vibrations are frequently recorded (Figs. 1, 2, middle strip, 4 top strip), much larger sonic vibrations are found with the same time relations to auricular systole. (Fig. 4, bottom strip.) In such cases, a presystolic physiological

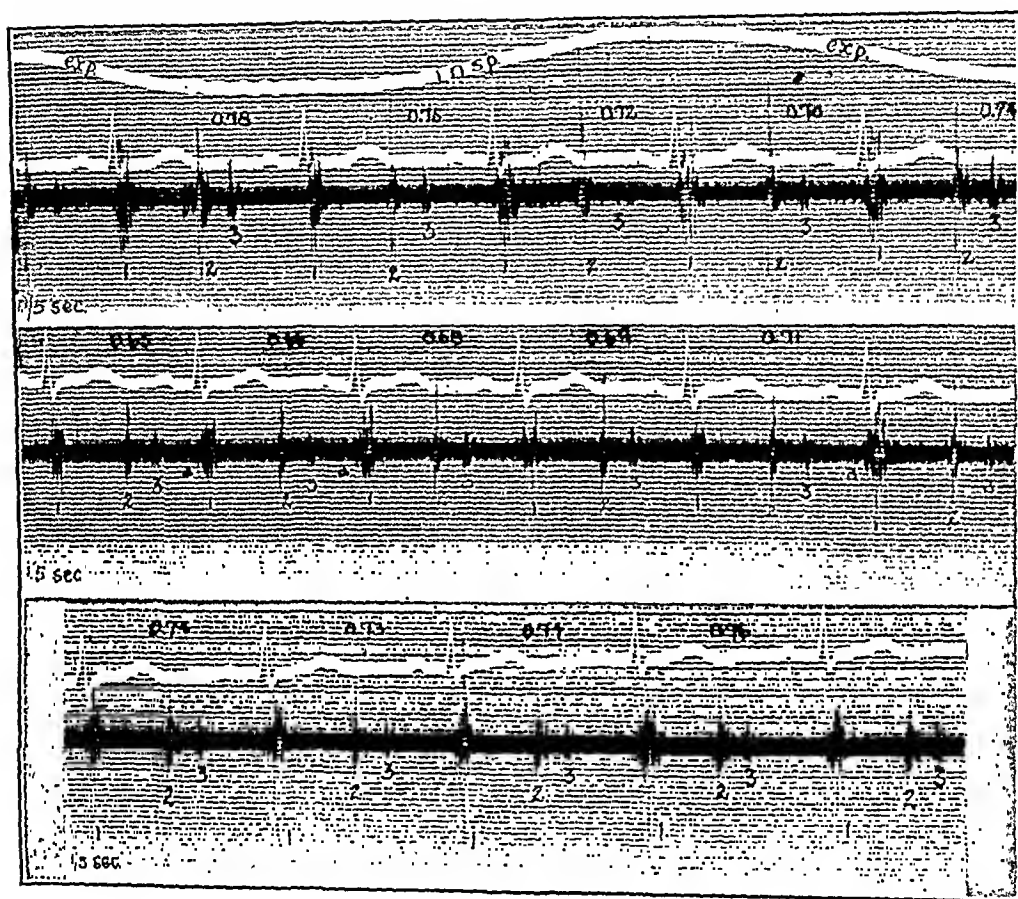


Fig. 2.—Physiological third heart sound. The top strip illustrates the effect of normal respiration. When the lungs were emptied, the third sound vibrations were decidedly larger than when the lungs were filled. On auscultation the sounds were likewise decidedly louder when the lungs were emptied. The lower two tracings were made with the breath held. The third sound vibrations are essentially the same throughout. The cycle lengths are given to show that the variations in cycle length in the top strip are not responsible for the variations in the third sound. In the second tracing subsonic presystolic vibrations (a) are recorded.

third heart sound is audible and has the same characteristics as the much more common presystolic gallop sound.

The time relations of the physiological third sound and gallop rhythm are comparatively simple. *In all of our 70 cases, without exception, the physiological third heart sounds and gallop sounds fell within one or both of two distinct time zones.* These time zones are: (1) the period of 0.10 to 0.21 second (usually 0.13 to 0.18 second) after the beginning of the second heart sound (unless the second sound is definitely split, under which circumstance the time relation is maintained with one component); and (2)

the period of 0.08 to 0.14 second after the beginning of the P-wave of the electrocardiogram.

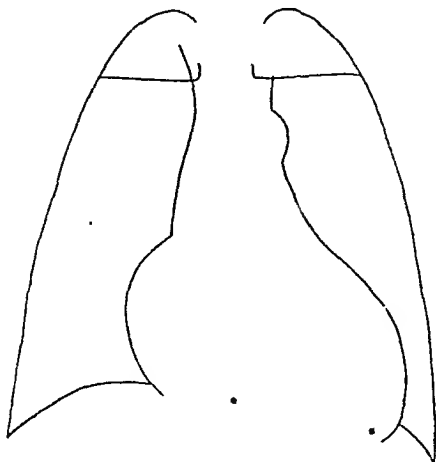


Fig. 3.—Orthodiagram made in a patient who exhibited both right and left-sided gallop rhythm. The dots represent the two positions over which the gallop sounds were best heard. The position with reference to the heart is determined by finding the point of maximum audibility of the gallop sound, fixing a lead disc on this point by adhesive tape, and marking its position on the anteroposterior silhouette by orthodiagraphy. Studies of this type made in fifteen cases of left-sided gallop all showed the gallop sound to have its maximum audibility near the apex.

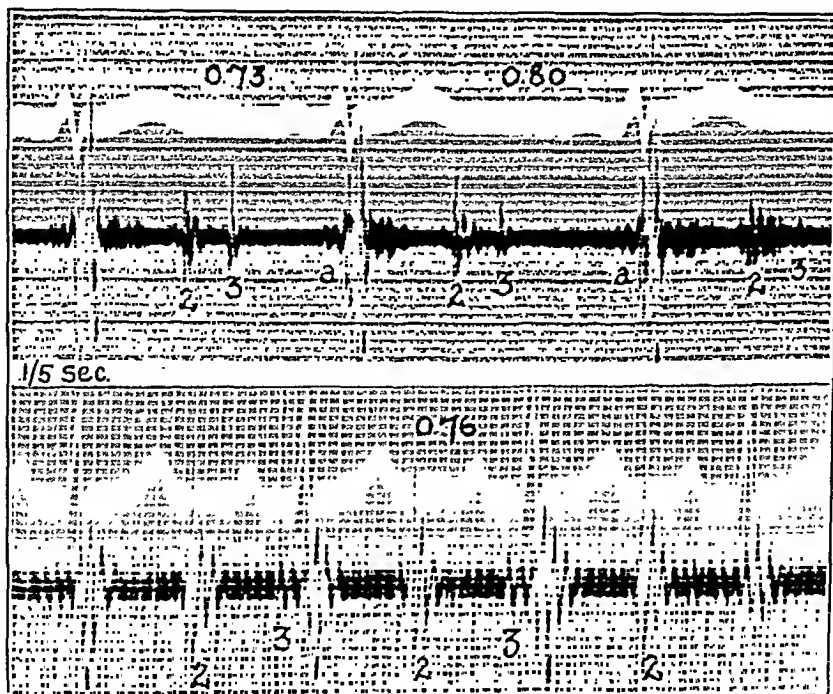


Fig. 4.—Physiological third heart sounds. The upper tracing illustrates protodiastolic third sound (3) and subsonic presystolic vibrations (a). The lower tracing shows presystolic vibrations (3) which were clearly audible as a presystolic physiological third heart sound.

Observations were made as to the effect of heart cycle length on the time relations of the sounds. In 20 cases exhibiting presystolic gallop rhythm, no correlation was observed between cardiac rate and the interval between

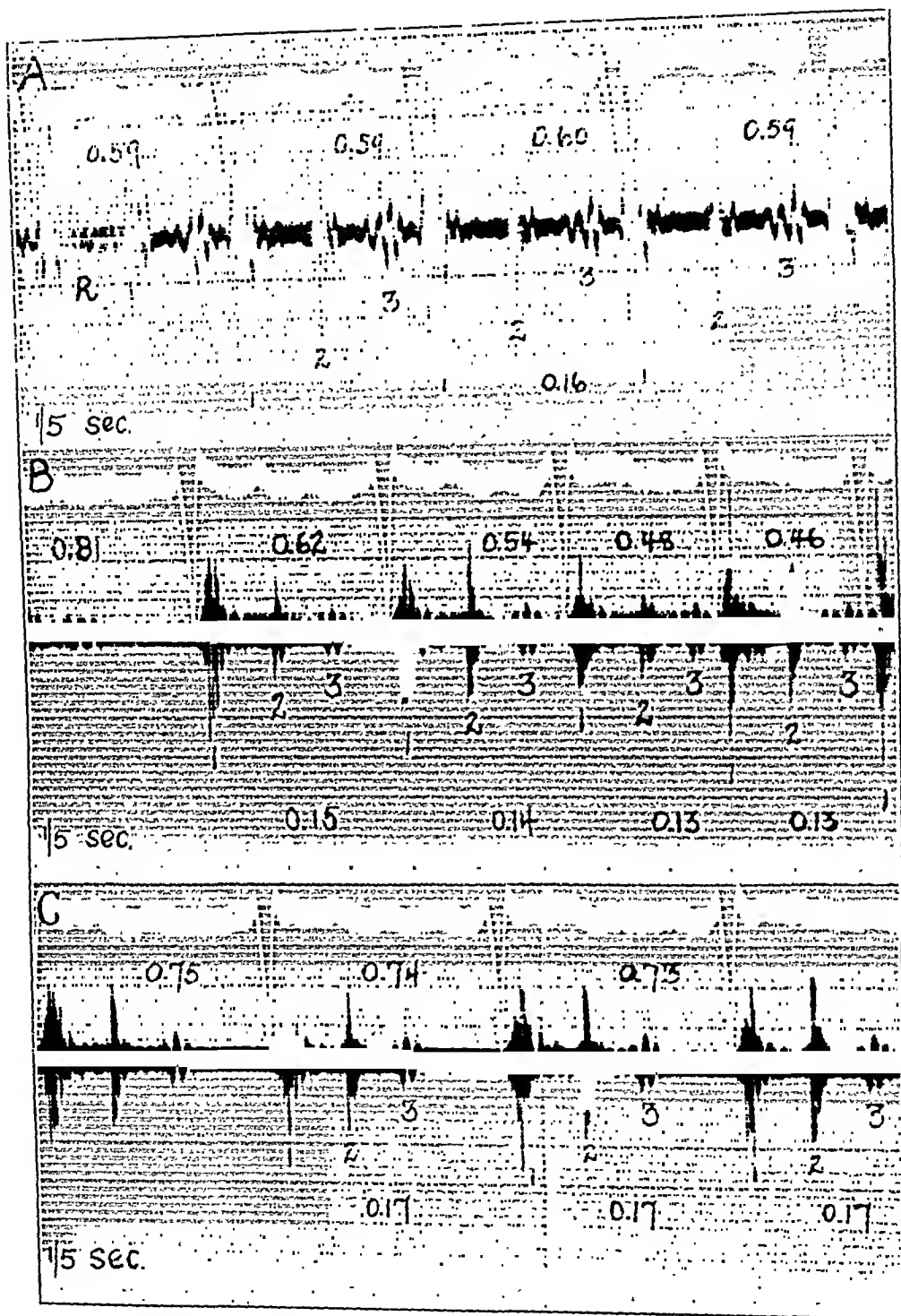


Fig. 5.—The top strip illustrates a somewhat imperfect summation gallop, the cardiac rate being approximately 100. Due to the imperfect summation, the gallop sound is prolonged. On auscultation the sound was easily heard but was not loud. The lower two strips were obtained from the same patient during auricular fibrillation. The gallop sounds were now clearly protodiastolic, shorter in duration, and faint, being heard with difficulty. There are variations in the duration of the interval between the second sound and the gallop sound (from 0.13 to 0.17 second) which shows some relation to the preceding cycle lengths.

the beginning of the P-wave and the gallop sound. In protodiastolic gallop rhythm, however, as in the case of protodiastolic physiological third heart sounds, evidence can be obtained that preceding cycle length is a factor in determining the duration of the interval between the second and protodiastolic sounds. This can be shown by studies of individual patients, comparing the intervals in sound tracings exhibiting different cardiac rates. The correlation between cardiac rate and the interval was not close for our entire group of cases; since the interval seems to be characteristically longer in some than in others. Doubtless, therefore, its duration is influenced by factors other than cardiac rate. In six cases of auricular fibrillation, exhibiting protodiastolic gallop rhythm, variations in this interval of from 0.02 to 0.04 second were noted, the shorter intervals tending to follow relatively short preceding cycle lengths, and the longer intervals relatively long preceding cycle lengths. There is, however, no accurate correlation between the duration of the interval and the preceding heart cycle. (Fig. 5.)

THE CLASSIFICATION OF GALLOP RHYTHM

What later came to be known as presystolic gallop rhythm was described by Charcelay⁹ in 1838. Bouilland¹⁰ gave it the name "bruit de galop." It remained for Potain,² however, to separate gallop from other sounds, and to classify the forms as protodiastolic, mesodiastolic and presystolic.

Our sound registration studies, as well as those previously made, confirm Potain's conception of protodiastolic and presystolic forms of gallop. These sounds have the time relations which have been mentioned above. The term presystolic is not strictly accurate, since the sound which it designates is not necessarily presystolic. Thus, when the auriculoventricular conduction time is prolonged, presystolic gallop is no longer actually presystolic in time. Its position depends on the time of auricular contraction.*

We have never observed a mid-diastolic gallop sound falling outside the time zones of presystolic or protodiastolic gallop. However, when these two zones merge because of tachycardia, a gallop sound may be present and fall near the middle of the diastolic period. Such a sound may occupy a position which is approximately mesodiastolic; however, it is just as near to the preceding beat as protodiastolic gallop and to the following beat as presystolic gallop. If either protodiastolic or presystolic gallop or both be present when the rate is slow enough to keep these time zones

*On account of the sanction conferred by long usage, it does not seem advisable to attempt to substitute another name for "presystolic gallop." Duchosal¹¹ has used the term "auricular gallop"; although this term has certain advantages it is likewise open to objection, since it might readily lead to the misconception that the sound originates within the auricles. Duchosal has emphasized the point that it should not carry such a connotation. A fault in nomenclature analogous to that of presystolic gallop is found in the strongly entrenched term "presystolic murmur," since this murmur, like the gallop sound, is dependent on auricular contraction. The presystolic murmur, however, tends to be more prolonged than a gallop sound so that a greater delay in A-V conduction is necessary to displace it from a presystolic position.

separate, a much louder gallop sound occurs when the rate increases and they become merged. This is equally true whether the merging be due to tachycardia (in which case the gallop sounds fall about the middle of diastole) or to lengthened A-V conduction time (which may cause the sound to be protodiastolic in time). Thus the term "mesodiastolic gallop," which connotes a type separate from protodiastolic and presystolic gallop, is misleading and should be discarded. We therefore propose that

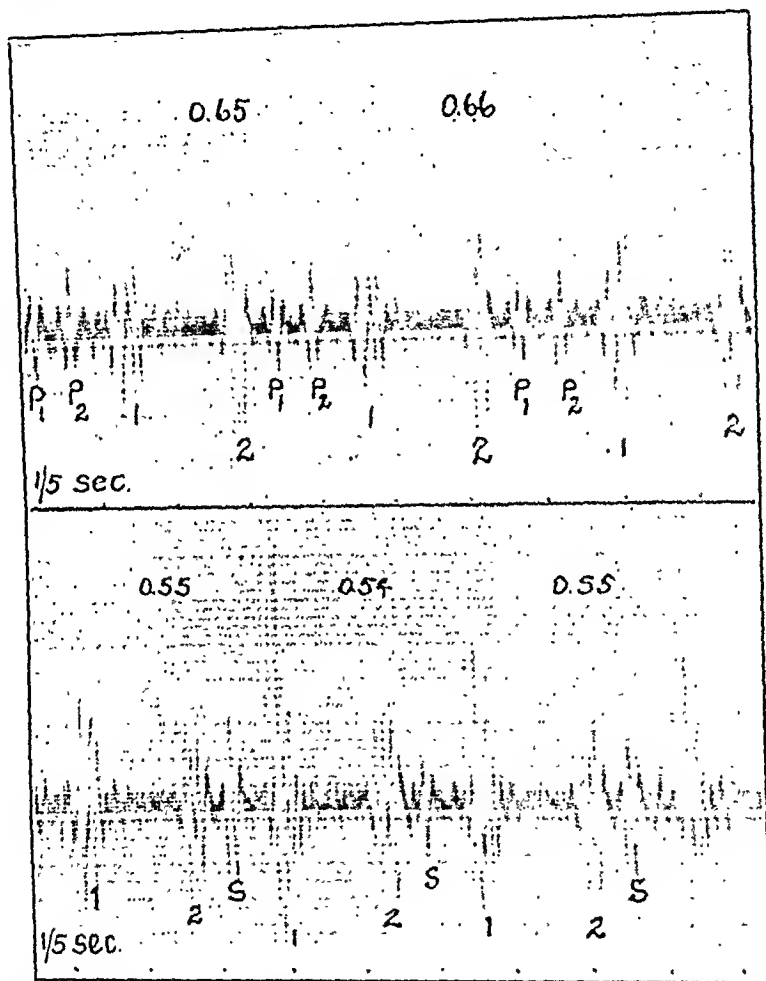


Fig. 6.—Minor grade heart-block, sinus arrhythmia and gallop rhythm. The upper tracing (taken during the period of retardation in rate) shows both protodiastolic (P₁) and presystolic (P₂) gallop. The lower tracing (taken during the period of acceleration in rate) which was part of a continuous strip with the upper shows the summation phenomenon (s). It is obvious from comparison with the second sound that the gallop sound vibrations are much larger when summation is present than when both protodiastolic and presystolic gallop are recorded as separate sound vibrations.

the type of gallop which occurs as a result of the coincidence of protodiastolic and auriculosystolic phenomena be called summation gallop.* The evidence for the occurrence of summation is based upon the effect of

*The term "summation gallop" was proposed by us in 1931 in the discussion of a classification of "extra" or additional heart sounds.¹² Summation (as used in psychology and physiology) is defined in Funk and Wagnall's dictionary as "The aggregate influence of several stimuli producing a sensible effect that no one alone would produce." It is in this sense that we apply the term rather than in accordance with its usage in physics (as summation tone).

rate changes, including sinus arrhythmia, auricular fibrillation, heart-block, ventricular and auricular extrasystoles on gallop sounds.*

1. *Effect of Variations in Rate.*—In two cases exhibiting both faint protodiastolic and presystolic gallop sounds when the heart rate was approximately normal, it was found that, as the heart rate was increased, there was a critical level at which the two gallop sounds merged, with the production of a single comparatively loud sound. When the heart rate again fell below the critical level, the loud gallop sound disappeared, being replaced by the two faint sounds originally present. In one of the cases

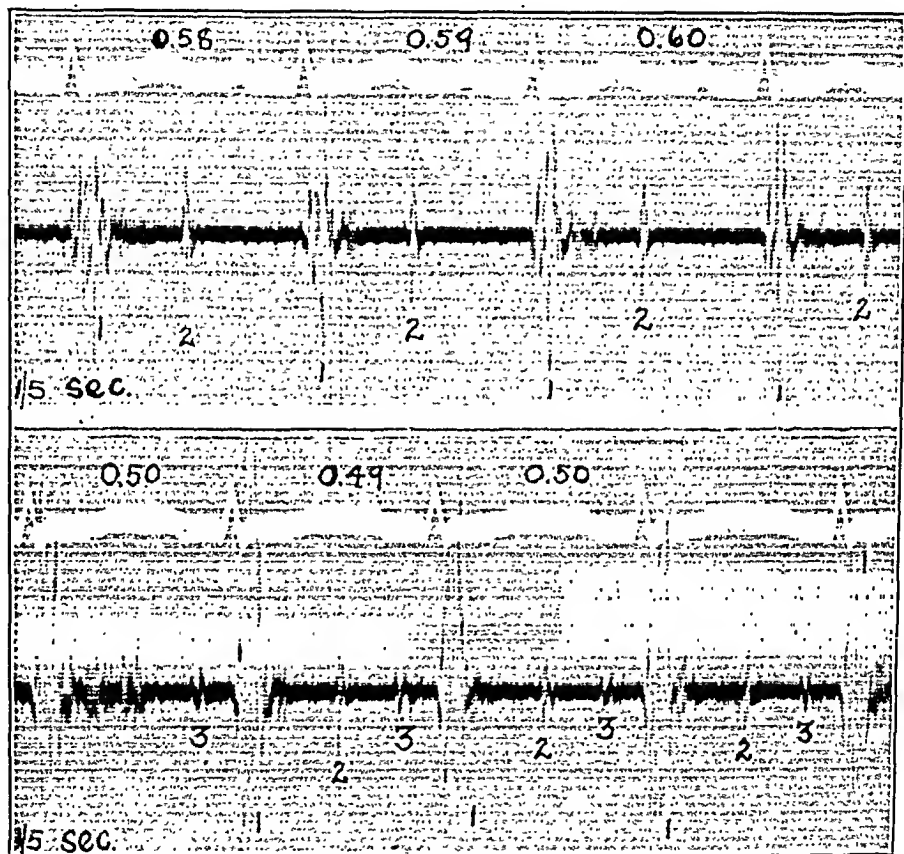


Fig. 7.—In the upper tracing the cardiac rate was 100, and no gallop sound was recorded. In the lower tracing made after elevating the rate to 120 by amyl nitrite so that auricular systole was superimposed on the protodiastolic phase of the preceding beat, a distinct gallop sound appeared.

the critical rate was sometimes attained during the phase of acceleration of sinus arrhythmia (Fig. 6).

It was repeatedly noted, both on auscultation and in sound tracings, that the critical level at which a gallop sound appears or, if already present (either presystolic or protodiastolic) suddenly becomes loud, is the rate at

*It has been shown that acceleration in the process of ventricular filling occurs in the protodiastolic period immediately after ventricular relaxation and also following auricular contraction. Most writers on gallop rhythm support the view that gallop sounds are in some way associated with waves of ventricular filling. Thus, when the two factors associated with acceleration of ventricular filling are superimposed, one might expect a single large surge of ventricular filling and therefore marked effects on gallop sounds. In a subsequent paper we shall present new evidence bearing on this point.

which auricular systole is superimposed upon the preceding protodiastolic period. (Fig. 7.) This rate in our cases was usually within the range of 100 to 130, depending on such factors as the length of the P-R interval and the duration of ventricular systole.* Doubtless also, the rapidity of isometric ventricular relaxation was a factor, but this could not be satisfactorily measured at rapid rates.† If the P-R interval was prolonged, the critical rate at which loud gallop sounds occurred tended to be lower. Thus in one case, with a P-R interval of 0.22 second, the critical level at which the loud sound appeared was between 90 and 100 beats per minute.‡

2. *Effect of Auricular Fibrillation.*—In three cases, heart sound studies were made during periods of regular rhythm and during auricular fibril-

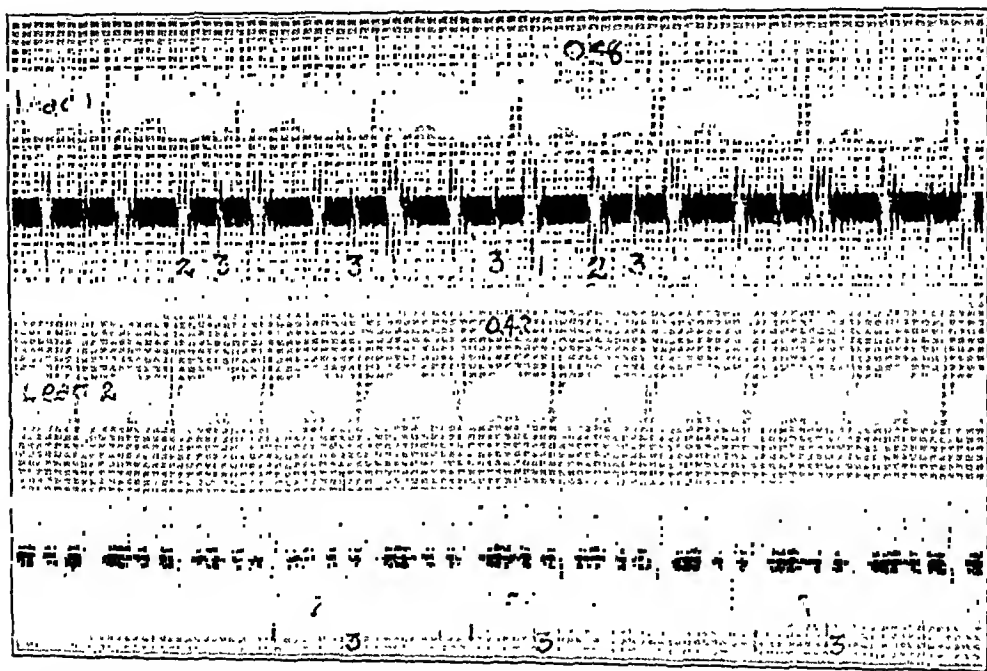


Fig. 8.—In the upper tracing the cardiac rate is 125 and summation gallop sound (3) is clearly recorded. The sound vibrations are smaller than those of either the first or the second heart sound. In the lower tracing (same patient but made on a different day) the rate is 143, and the vibrations of the gallop sound are of larger amplitude than either the first or second sound. The interval between the second and gallop sound (0.10 second) is the shortest recorded in this study. The shorter interval in the lower strip is probably due to the greater rate.

lation. In one of these cases, during normal rhythm the critical rate at which a loud gallop sound appeared was approximately 100. In the other two cases the critical rate was not determined, but the gallop sound was loud at rates of 107 and 114. In all three, however, auricular systole was

*The lowest rate at which summation occurs is not necessarily the optimum rate for the production of the loudest gallop sound. (Fig. 8.)

†The ventricular isometric relaxation phase is measured by the interval between the beginning of the second heart sound (provided the sound is not split) and the beginning of the descending limb of the V-wave in the optically recorded venous pulse in the neck. When auricular contraction falls in the protodiastolic period, the significant point in the V-wave tends to be obscured by the coincident A-wave.

‡In connection with these observations it should be emphasized that, irrespective of superimposition of auricular contraction on the preceding protodiastolic period, acceleration in rate may accentuate gallop or physiological third heart sounds, or if they are absent at slower rates, cause them to appear. In the absence of summation, however, the effect of rate changes is not so striking.

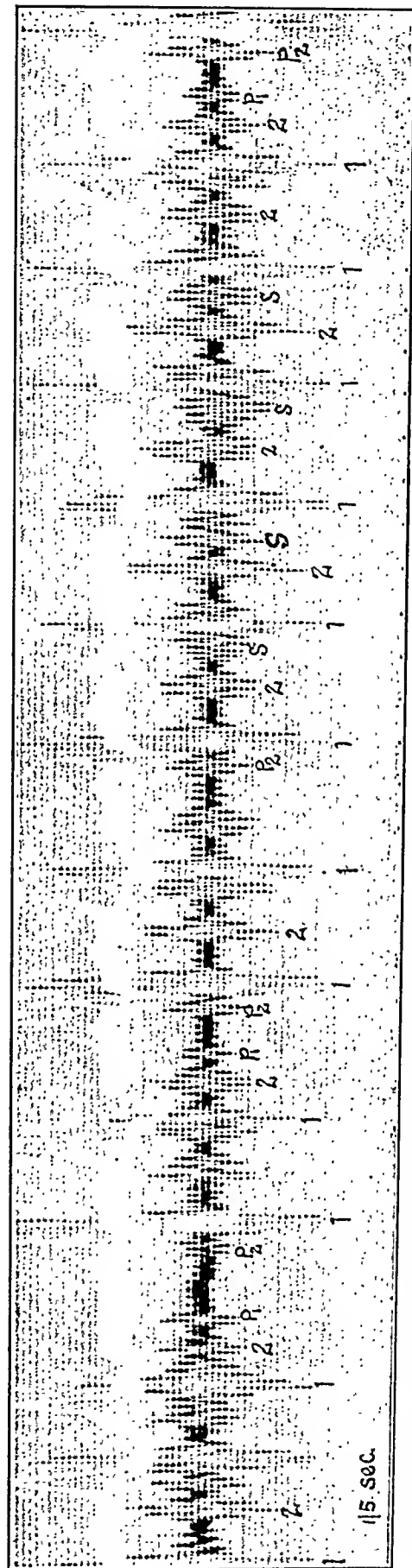


Fig. 9.—During regular rhythm, summation gallop (S) is present. During the compensatory pause following an extrasystole both a protodlastolic (P₁) and a presystolic (P₂) gallop sound are present.

superimposed on the protodiastolic zone. During auricular fibrillation in the three cases, only faint protodiastolic gallop sounds were heard irrespective of the cardiac rate or the length of the preceding heart cycle. (Fig. 5.)

3. *Effect of Incomplete Heart-Block.*—The effect of variation in position of auricular contraction on the intensity of gallop sounds was carefully studied in one case of incomplete heart-block. In this case the differences in loudness of gallop sounds in successive beats was striking. The sound tracings showed their time incidence to be in a range of 0.12 to 0.14 second after the second heart sound. When the P-wave began in a range of 0.02 second before to 0.02 second after the second heart sound, the gallop sound attained its maximum intensity. When the P-wave fell outside but near this zone, either before or after it, the gallop sounds were of moderate

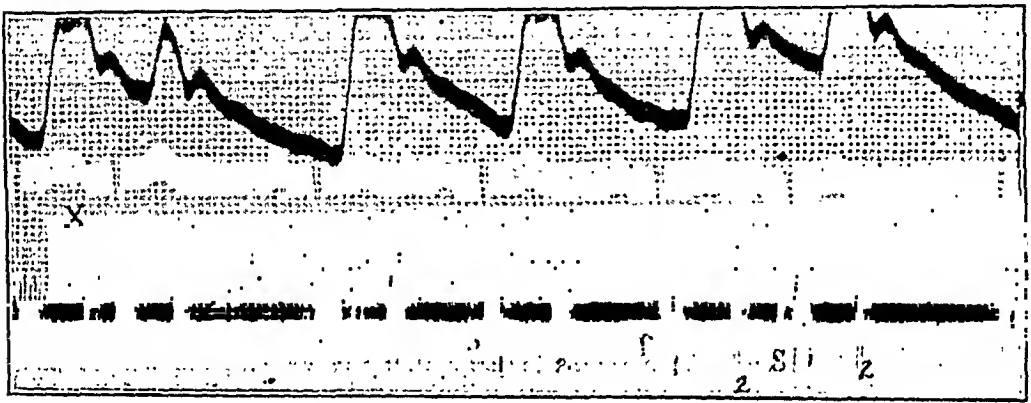


Fig. 10.—During regular rhythm, no protodiastolic disturbance is recorded, but there are small subsonic presystolic vibrations (p). In connection with certain premature auricular beats a single summation gallop sound (S) is recorded. When the auricular beat is highly premature (X), no gallop sound occurs, possibly because of curtailment of the protodiastolic phase.

intensity. When, however, the P-waves were far removed from the zone, the gallop sounds were comparatively faint. (Fig. 1.)

4. *Effect of Ventricular Extrasystoles.*—In three cases with rapid rates, loud gallop sounds and extrasystoles, the loud gallop sound failed to appear during the compensatory pauses succeeding premature beats, but in each case during such pauses there were present either protodiastolic or presystolic gallop sounds or both. On resumption of the rapid regular beating the loud gallop sound immediately recurred. Thus when auricular contraction was separated from the protodiastolic zone (as occurred during the compensatory pauses), the loud single gallop sound was replaced by less loud protodiastolic or presystolic sounds, or both. (Fig. 9.)

5. *Effect of Auricular Extrasystoles.*—In one case with auricular extrasystoles, there was present (while the rhythm was regular) a faint presystolic gallop sound, which began 0.14 second after the beginning of the P-wave. There was no protodiastolic gallop. When premature auricular beats occurred, there was a louder gallop sound which fell 0.14 second after the beginning of the aberrant premature P-wave and 0.20 to 0.23 second

after the beginning of the second heart sound. (Fig. 10.) In another case exhibiting auricular extrasystoles there was (during regular rhythm) a protodiastolic gallop sound, but the tracing also showed small waves (probably subsonic) at the time presystolic gallop might have been expected. When auricular extrasystoles occurred so that the premature auricular beats were superimposed on the protodiastolic period of the preceding beat, a loud gallop sound invariably occurred. Thus even the superimposition of an aberrant auricular contraction on a protodiastolic zone is capable of producing the summation phenomenon. (Fig. 11.)

It seems entirely probable that the summation effect influences the third heart sound in the same way that it does gallop rhythm, although little opportunity presented itself to test this point. In certain cases the third sound did not appear until the rate was rapid enough for summation to occur. In a young varsity oarsman with auricular extrasystoles, some transmitted and others blocked, the third sounds were heard and recorded only when the aberrant auricular beat fell in the range of ventricular

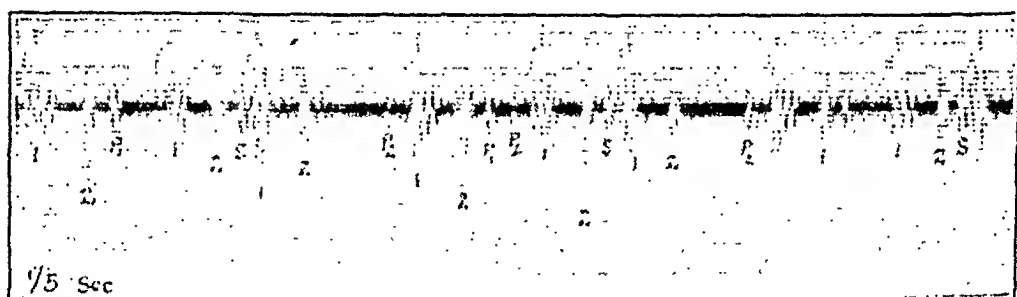


Fig. 11.—Protodiastolic (P_1) and presystolic (P_2) gallop sound vibrations (the latter subsonic) when beats are of normal type. Summation gallop (S_1) with vibrations of much larger amplitude when premature auricular beats occur.

protodiastole, irrespective of whether or not the extrasystole was blocked. Thus the mechanism was similar to that illustrated in Fig. 11.

From the above observations it is apparent that when auricular systole becomes superimposed on the protodiastolic zone of the preceding beat, a gallop sound may either appear for the first time, or if already present, become greatly intensified. This intensification occurs irrespective of whether the preceding gallop sound or sounds had been presystolic, protodiastolic or both.

The hypothesis of summation gallop is therefore consistent with the behavior of gallop rhythm under all the tests to which it was subjected. Furthermore, it appears to offer a rational explanation for some of the supposed vagaries of gallop rhythm (such as its comparatively frequent occurrence during tachycardia and during minor grade heart-block).

THE INCIDENCE OF THE VARIOUS TYPES OF GALLOP RHYTHM

The comparative frequency of the various types of gallop rhythm has been discussed by various writers, and statistics have been compiled based

on auscultatory findings. Not much confidence can be placed in these figures, not only because of unsatisfactory classification, but also because of the practical difficulty of accurate perception of time relations that presents itself in many cases without simultaneously recorded sound tracings and electrocardiograms.

Among our 60 cases, 14 showed only protodiastolic gallop while they were under observation and 22 only presystolic gallop. The summation form was recorded in 24. In 7 of these, due to constant tachycardia during the period of observation, no other manifestation of gallop was recorded. In the other 17, however, many of whom were under observation for extended periods of time, the findings were variable. When the rate slowed so that summation was no longer present, one of the following was recorded: (1) no gallop sound; (2) presystolic gallop alone; (3) protodiastolic gallop alone; or (4) both presystolic and protodiastolic gallop. It is of interest that in 13 of the 17 cases, both presystolic and protodiastolic gallop were recorded (occurring either together or singly at various times). Analysis of all our tracings in the 60 cases revealed the fact that at one time or another 29 had protodiastolic gallop and 37 presystolic gallop.

Although the number of cases studied is far too small for statistical purposes, the figures appear to indicate that there is no great difference of incidence between protodiastolic and presystolic gallop. Previous studies are contradictory regarding this point. Thus recently it has been stated that "when differentiation is possible, it is found that the protodiastolic gallop rhythm is much more common than any other timing, being perhaps six times more common than the presystolic type while the mesodiastolic type is rarer still than the presystolic. . . ." ¹³ Other writers believe that presystolic gallop is more common than protodiastolic.

The unmistakable tendency for both presystolic and protodiastolic gallop to occur in the same case deserves emphasis. Isolated case reports of this association are available in the literature. The fact, however, that in 13 of our 60 cases both protodiastolic and presystolic gallop were recorded establishes the close relationship between these two. Furthermore, it seems probable that if our studies of the various cases had been extended over longer periods of time, more might have shown this association.*

Among the 10 cases classified as having the physiological third heart sound, the third sound was protodiastolic in 9, a presystolic sound was heard in only 1 case, despite the fact that small presystolic vibrations were registered in several.

RIGHT-SIDED GALLOP RHYTHM

Potain^{2, 14} was the first to describe right-sided gallop rhythm. He pointed out that in right-sided gallop, the gallop sound is heard best, not at the apex, but in the neighborhood of the xyphoid cartilage. Potain associated

*These observations tend to support Potain's view that the various types of gallop rhythm are closely related.

right-sided gallop rhythm with dilatation of the right side of the heart and tricuspid insufficiency, but believed that the underlying disease causing right-sided cardiac dilatation was usually "gastro-hepatic." He also stated that it tended to occur in patients with chlorosis.

Several cases of right-sided gallop have been reported since Potain's original observations, but some writers still believe that it is unsafe to state that right-sided gallop can be distinguished from left-sided gallop. Pezzi¹⁵ believes that the usual gallop is in all probability produced in both sides of the heart.

Among our 60 cases which exhibited gallop rhythm, the localization was always right-sided in 3, and sometimes right-sided and sometimes left-sided in two. In 3 of the 5 cases the extra sound was protodiastolic; in one it was sometimes protodiastolic and sometimes presystolic; while in one, summation gallop was present. The patient with right-sided summation gallop had advanced pneumoconiosis and right-sided heart failure. At necropsy the right ventricle was found to be greatly dilated and the left ventricle little if any changed in size. In one of the two cases with only right-sided protodiastolic gallop, a clinical diagnosis of right-sided heart failure was made because of severe congestive phenomena from which, however, the lungs seemed to be spared. The other had hyperthyroidism, auricular fibrillation and a very rapid ventricular rate. In this case, however, we were unable to determine whether there was disproportionate damage on the two sides.

The two patients who exhibited both right and left-sided gallop were in states of profound decompensation. One, during a short period, exhibited both right and left-sided gallop simultaneously. The other patient exhibited left-sided gallop for a time, then right-sided gallop and finally left-sided gallop again. During the period that right-sided gallop was present, there was no pulmonary congestion discoverable but there was marked engorgement of the veins of the neck, congestion of the liver, and edema, this clinical picture suggesting a predominately right-sided heart failure. At necropsy both the right and left ventricles were found greatly dilated.

These observations have left no doubt in our minds that there is a type of gallop rhythm which may properly be termed right-sided. This is based on (1) auscultatory localization of the gallop sound, (2) the fact that the localization can be confirmed by sound registration studies, and (3) the occurrence of predominantly right-sided heart failure in cases exhibiting the right-sided localization of the sounds.

On the basis of the present status of our knowledge regarding physiological third heart sounds and gallop rhythm the following schema of classification is proposed:

SCHEMA OF CLASSIFICATION

1. *Physiological Third Heart Sounds*.—(Occur commonly in children and young adults with no evidence of cardiovascular damage nor signifi-

cant alteration in cardiac function. The sounds are characteristically dull, low-pitched, and are heard best near the apex.)

(a) Protodiastolic.—Fall in the protodiastolic time zone, usually beginning 0.12 to 0.21 second after the beginning of the second heart sound. Nearly all cases belong to this group.

(b) Presystolic.—Bear a definite relation to auricular contraction. Begin 0.08 to 0.14 second after the beginning of the P-wave of the electrocardiogram. While small vibrations are commonly found in sound tracings, it is only rarely that sounds can be heard.

(c) Summation Form.—Occur only when time zones of protodiastolic and presystolic sounds are merged because of tachycardia, sinus arrhythmia or auricular extrasystoles.

2. *Gallop Rhythm*.—The term "gallop rhythm" is to be applied only when there is evidence of cardiovascular damage or significant alteration in cardiac function. The sounds are characteristically dull and low-pitched. Gallop sounds are usually left-sided and are heard best over or near the apex, but occasionally may be right-sided and heard best near the xyphoid.

(a) Protodiastolic.—Fall in the protodiastolic time zone usually beginning 0.12 to 0.21 second after the beginning of the second heart sound. Usually left-sided but occasionally right-sided.

(b) Presystolic.—Bear a definite relation to auricular contraction. Begin 0.08 to 0.14 second after the beginning of the P-wave of the electrocardiogram.* The right-sided type is very rare.

(c) Summation.—Occur only when the time zones of protodiastolic and presystolic gallop sounds are merged, because of tachycardia, heart block, sinus arrhythmia or auricular extrasystoles.

We believe that the above modification of Potain's classification has the following advantages:

1. The so-called mesodiastolic gallop is discarded, since no justification has been found for it as an entity apart from protodiastolic and presystolic

*In a recent paper Duchosal¹¹ has discussed the time relations of the P-waves of the electrocardiogram and auricular (presystolic) gallop sounds. Since the values which he reports differ considerably from those obtained by other workers, including ourselves, it becomes necessary to analyze such evidence as is available in the attempt to account for this discrepancy. Thus Duchosal, measuring from the peak of the P-wave to the beginning of the gallop sound, found the range of these intervals to be -0.02 to +0.14 second. Since the peak of the P-wave usually falls 0.03 to 0.06 second after the beginning of the P-wave, it is obvious that Duchosal's range of values is much wider than ours. This is of special interest in connection with the short intervals, since Duchosal believes that these have a bad prognostic significance. In his paper we find five figures to illustrate extremely short intervals between the peak of the P-wave and the gallop sound. In his Figure XI, the only one of the five in which the vibrations regarded as auricular (presystolic) gallop are not open to a question of interpretation, the time relations are within conventional limits, the interval between the beginning of the P-wave and the gallop sound being 0.08 second. In his Figure IV the interval is also 0.08 second, but since the gallop sound falls only 0.16 second after the second sound it is also within the range of protodiastolic gallop. In his Figure X, the vibrations regarded as representing gallop fall only 0.04 second after the beginning of the second sound. Even with the most extreme grades of tachycardia, the interval is rarely less than 0.12 second, and in our experience has never been less than 0.10 second. The interval of 0.04 second would therefore have to be regarded as almost impossible for gallop rhythm although well within the range of a split second sound. In his Figures XII and XIII in which the time intervals between the beginning of the P-wave and the gallop sounds are very short (in Figure XIII only 0.02 second) the time relations to the second sound correspond to what is expected in protodiastolic gallop. Thus in our opinion Duchosal has not demonstrated the existence of very short time intervals (less than 0.08 second) between P-waves and presystolic or auricular gallop sounds.

gallop. A source of confusion in the understanding of gallop rhythm and its classification has therefore been removed.

2. The hypothesis of summation is in accord with all known facts regarding gallop rhythm and the physiological third heart sound. Its use makes classification sharply definitive, so that there is no difficulty in fitting cases into their proper categories. Furthermore, certain of the supposed vagaries of gallop rhythm are reasonably accounted for by this hypothesis.

DIFFERENTIAL DIAGNOSIS

The characteristics of gallop rhythm and the physiological third heart sound which have been described above are sufficiently distinctive to make possible their differentiation from all other groupings of heart sounds. In the great majority of cases purely clinical methods are adequate, no apparatus except a stethoscope being required. It is necessary to pay attention to the localization of sounds, their pitch, duration, and timbre. For these purposes, auscultation is far superior to any of the sound registration devices now available. In addition the examiner should educate himself to some appreciation of the differences in duration of short intervals. Accurate timing by graphic methods, although a satisfactory procedure, is necessary for diagnosis in only a small minority of cases.

In our experience the following sounds have been confused with either gallop or physiological third heart sounds:

(1) The opening snap of mitral stenosis; (2) mid-diastolic murmur; (3) presystolic murmur; (4) reduplicated first heart sound; (5) reduplicated second heart sound.

(1) We have recently reported a study of the characteristics of the opening snap in mitral stenosis.³ It is differentiated by the following: (a) It occurs only in mitral stenosis, whereas gallop rhythm is very rare in mitral stenosis and does not occur if the stenosis is well developed. (b) It is a short, sharp sound. (c) Its point of maximum audibility is in the third or fourth interspace over the body of the heart and not at the apex. (d) It tends to fall closer to the second sound, although the longest intervals overlap the shortest intervals in gallop rhythm or the physiological third sound. There is, however, a fundamental difference in time relations since the opening snap occurs before ventricular filling has begun; whereas gallop and third sounds always fall near the summits of waves of ventricular filling. Occasionally the diagnosis cannot be decided by clinical methods. Under such circumstances a simultaneous record of heart sounds and apex cardiogram will be necessary for differentiation.

(2) Mid-diastolic murmurs sometimes occur in mitral stenosis when the rate is rapid. On superficial examination these may simulate the summation type of gallop rhythm. However, the utilization of the various methods for influencing gallop sounds and diastolic murmurs (changes in position, cardiac rate, exertion) usually makes differentiation possible.

The gallop sound retains its characteristics, particularly that of being fairly quickly damped, although its loudness may change considerably, whereas the murmur tends to be prolonged and has a decrescendo quality. Furthermore, gallop sounds are heard best nearer the apex than the murmurs of mitral stenosis. In doubtful cases the presence of other signs suggesting mitral stenosis is strong presumptive evidence for the murmur. Simultaneous graphic records of sounds and apex cardiogram show that the murmur of mitral stenosis begins at the onset of ventricular filling rather than at the summit of the wave.

(3) In several of our cases, presystolic gallop sounds were mistaken for presystolic murmurs of mitral stenosis. In no instance was a presystolic murmur mistaken for gallop. The presystolic gallop is a low-pitched short sound usually clearly separated from the first sound (unless the A-V interval is very short), whereas presystolic murmurs tend to be longer in duration and crescendo in quality running up to the first sound. The differentiation can usually be made by the auscultatory characteristics including localization of the sounds, but the presence or absence of associated signs of mitral stenosis is also an important differential point.

(4) The clinical differentiation between presystolic gallop and reduplication of the first heart sound is occasionally difficult and in certain cases impossible. The quality of sounds and location do not offer dependable criteria for differentiation. The time relations are most important. Thus in some cases it can be determined that the sound is actually presystolic, coming before ventricular contraction. Another point of value is the interval between sounds. In reduplication of the first sound, this interval does not tend to exceed 0.07 second even in cases of bundle-branch block. In most cases of presystolic gallop rhythm, the intervals range between 0.08 and 0.14 second. When A-V conduction defects are present, the intervals are still longer. If, however, the P-R interval is short (0.12 to 0.14 second) the split between the gallop and first heart sound may be no wider than that of reduplicated first sounds. Thus a wide split between sounds constitutes strong evidence for gallop rhythm; a narrow split has no value as a differential point. Under these circumstances a simultaneously recorded sound tracing and electrocardiogram may be necessary for a decision.

(5) Reduplicated second sounds are easily differentiated from protodiastolic or summation gallop rhythm and physiological third sounds by the following characteristics: (a) Reduplication of the second sounds may occasionally be well heard at the apex, but its maximum audibility is at the base and rarely as low as the fourth interspace. (b) Second sounds are shorter, sharper and higher in pitch than gallop sounds. (c) The intervals between the two components of split second sounds are appreciably shorter than those between second sounds and gallop rhythm.

There are three other types of sound which should be mentioned in the

differential diagnosis. These are (a) pericardial frictions; (b) the rather common clicking sounds which fall between the first and second heart sounds,* and (c) the so-called systolic gallop sounds. Friction sounds are differentiated by their characteristic rough or scratching quality and the fact that they are usually heard both in systole and in diastole, tending to be loudest during systole. Systolic gallop and the systolic clicking sounds both fall between the first and second heart sounds. The clicking sounds have no resemblance to gallop sounds, and the differences in quality are sufficient to differentiate them. Systolic gallop sounds, however, are similar in quality to the types of gallop which occur during diastole. Their occurrence during systole and the fact that they are heard best over the aortic area clearly differentiate them.

SUMMARY

1. The only available criterion for distinguishing between physiological third heart sounds and gallop rhythm is the status of cardiac function. Both types of sound are accentuated by the same procedures. They have similar time relations, quality and intensity. Their positions of maximum audibility are identical except that right-sided physiological third heart sounds are unknown.

2. Gallop and physiological third heart sounds invariably fall in either the protodiastolic or the auriculo-systolic time zone.

3. When these two time zones become superimposed, either as a result of tachycardia, minor grade heart block, sinus arrhythmia or auricular extrasystoles, gallop sounds may either appear for the first time, or, if already present, become markedly accentuated. This effect is so pronounced as to constitute a summation phenomenon.

4. The hypothesis of summation is in accord with all known facts regarding gallop rhythm. Moreover, it offers a reasonable explanation for some of the variations in gallop sounds hitherto unaccounted for.

5. A classification of physiological third heart sounds and gallop rhythm, based on Potain's classification of gallop rhythm, but altered to correspond with objective phenomena, is proposed. The erroneous concept of mesodiastolic gallop is discarded, and summation gallop is recognized. The classification abolishes the practical difficulties, heretofore encountered so frequently, in placing cases into proper categories.

6. There appears to be no great disparity in the incidence of presystolic or protodiastolic gallop. Summation gallop is little if any less frequent. It can be produced in cases with either of the other types of gallop, or in cases with a predisposition to gallop, by the simple expedient of accelerating the cardiac rate enough to bring about superimposition of protodiastolic and presystolic events.

7. Potain's conception of right-sided gallop rhythm, disputed by certain

*We have designated these sounds "mid-systolic clicks."

observers, has been confirmed by our investigations. It tends to occur in cases exhibiting predominantly right-sided heart failure.

8. In the differential diagnosis of gallop rhythm and the physiological third heart sound, errors have been encountered involving one or another of the following: (1) the opening snap of mitral stenosis; (2) mid-diastolic murmur; (3) presystolic murmur; (4) reduplicated first heart sound; (5) reduplicated second heart sound. Other possible sources of error are (a) pericardial friction sound; (b) mid-systolic click; and (c) the so-called systolic gallop rhythm. In the great majority of cases differentiation is possible by clinical methods alone. In occasional cases, however, accurate timing requiring graphic methods is necessary.

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P-WAVE CHANGES IN ACUTE CORONARY ARTERY OCCLUSION*

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CHANGES in the P-wave of the electrocardiogram during an attack of acute coronary artery thrombosis seem not to have been reported. That a definite change occurs, however, in the auricular complex will be demonstrated by a review of the last forty cases treated at the New York Hospital, New York. A typical example will illustrate these changes in the P-wave.

CASE 1. (301,532) A Greek, forty years of age, was admitted to the New York Hospital at 10 P.M., October 11, 1931, for severe precordial pain. That day, about one hour after his lunch, the patient commenced to have precordial pain which radiated to the back and down the left arm to the finger tips. He rested in bed, his symptoms abated, and after supper he went for a walk. The pain suddenly returned with great severity, and he immediately took a taxicab to the hospital. The physical examination on admission revealed a well nourished and well developed individual "writhing and twisting with pain" and with a cyanotic grayish color. The heart was regular, the rate 66 beats per minute, and the heart sounds were faint. The patient was very sick. He was dyspneic, the precordial pain was marked, sweating was profuse, the lungs were congested at the bases, the patient coughed. Because of the severe precordial pain, morphine sulphate was administered in one-fourth grain doses every four hours until the fifth day after admission when only one dose was given. On the sixth day the patient was definitely better, but there were still some pain, sweating and restless sleep. The next day was his first "comfortable day." The temperature on the day of admission was 99° F., on the third day it was 103° F., and then it gradually fell to 99° F. on the eleventh day. The pulse rate corresponded to the temperature, ranging from 120 beats per minute on the third, to 60-70 per minute on the ninth day. The blood count on the third day in the hospital disclosed a leucocyte count of 15,300 with a polymorphonucleosis of 81 per cent, but on the seventh day the count was normal. The blood Wassermann test was negative. The urine was normal. On the day after admission the blood pressure was 100/80 mm. Hg, and at the time of discharge from the hospital it was 120/70 mm. Hg. A teleroentgenogram of the chest, which was taken October 16, 1931, the sixth day, showed an enlarged heart with a concentrically hypertrophied left ventricle, and showed also signs of chronic passive congestion in the lungs. On November 4, 1931, in a second film, the lungs were clear. The patient convalesced uneventfully and was discharged from the hospital on November 6, 1931, with the diagnosis of thrombosis of the coronary artery.

The first electrocardiogram was taken October 13, 1931, less than forty-eight hours after admission. It showed a normal sinus rhythm, rate about 100 beats per minute (Fig. 1). The voltage of the QRS group was moderately low. The striking features were the abnormal S-T intervals and the large P-waves. In subsequent records the rate became slower, the voltage of the QRS gradually higher, the T-waves in Leads I and II became

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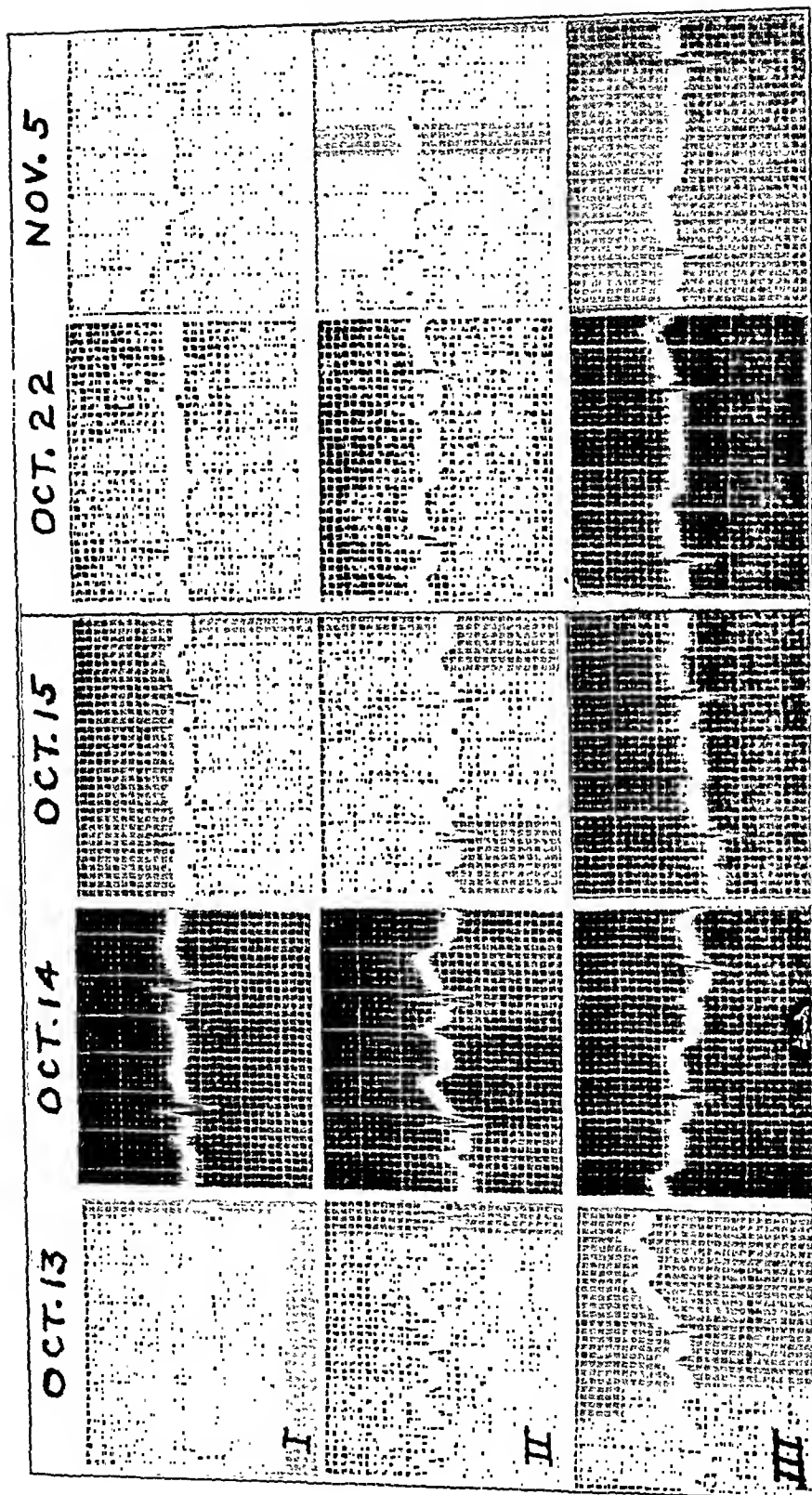


Fig. 1.—Attack of acute coronary artery occlusion October 11, 1931. Note large P-waves on October 13, the third day of illness. On October 14, P-waves practically unchanged. On October 15, fifth day, P-waves return to normal size and remain so until discharge from hospital November 5, 1931.

inverted and the S-T intervals normal. The P-waves remained large for three days and then gradually diminished, reaching a fixed size about the fifth day (Fig. 1).

In 32 cases out of the 40 studied there were similar changes in increased size of the P-waves during the early days of the acute coronary artery thrombosis (Table I). The P-waves were not only relatively enlarged but

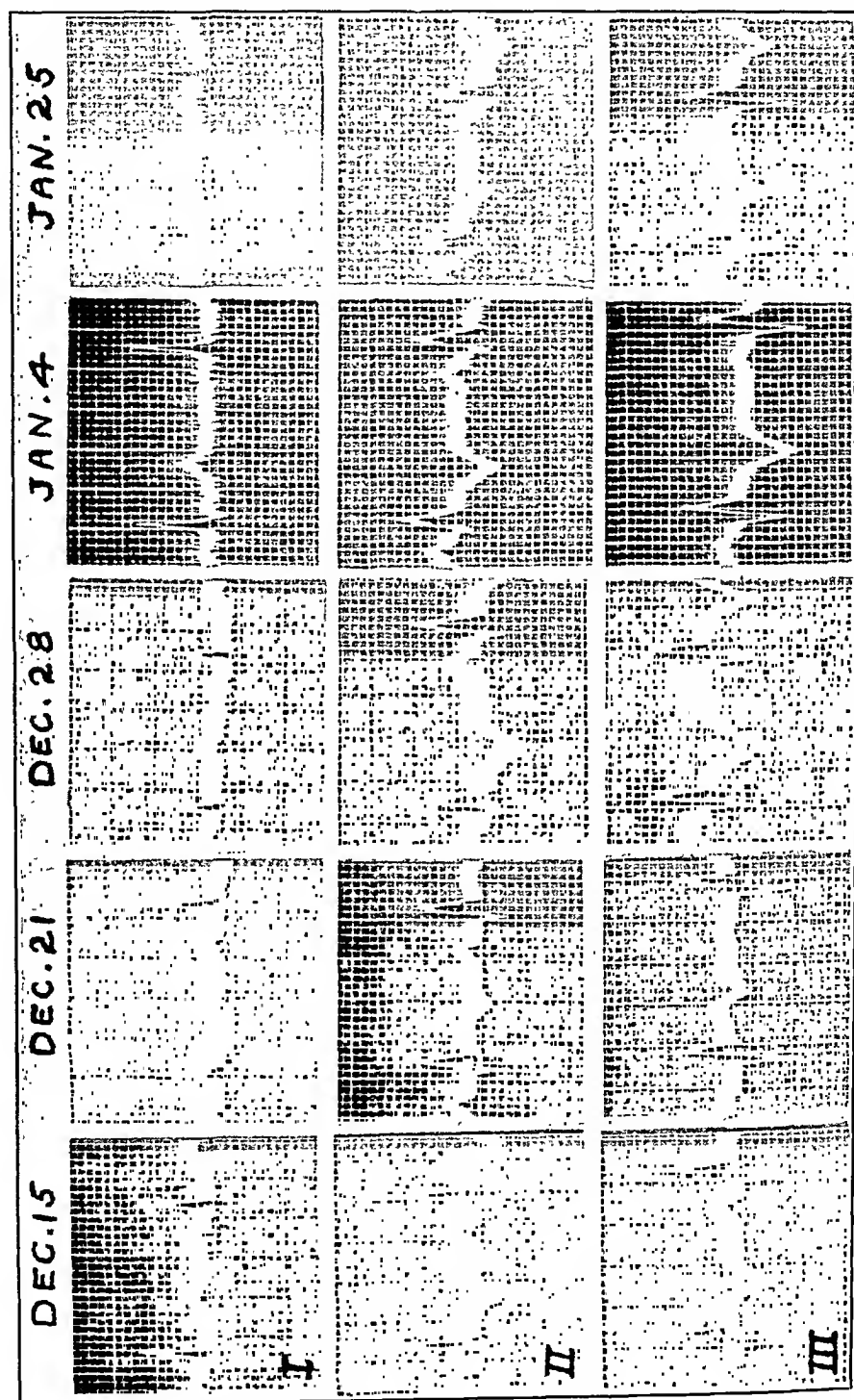


Fig. 2.—Attack of acute coronary artery occlusion December 15, the third day of the attack. P-waves return to normal size on December 21, the ninth day.

often absolutely increased as well. In normal individuals the P-wave is under 2 mm. in height in any lead. Lewis and Gilder¹ in 52 normal people found that the P-wave was never 2 mm. high; i. e., the maximum was

1.7 mm., and the average height of the P-wave was 1.16 mm. in Lead II, the derivation in which it was highest. Pardee² considers a P-wave of 2 mm. or more to be abnormal. In a series of 250 normal individuals on whom we took electrical tracings at Cornell University Medical College, only eight individuals had auricular complexes of 2 mm. height (3 per cent), whereas among the forty patients under consideration there were actually sixteen individuals whose P-waves measured 2 mm. or more in the first days of their illness, a percentage of 40 (Table I).

It is felt that, unlike the P-wave in mitral stenosis, the auricular complex in acute coronary artery thrombosis varies primarily in amplitude. It is usually a sharply peaked wave (Figs. 1 and 2). Occasionally, however, the P-wave becomes wide and notched or has a double summit. In four of our patients notching occurred; in two cases the P-wave became both wide and notched. In only one of these six cases was the amplitude increased. These variations occurred during the early days of the coronary artery closure, just as did the variations in size.

Not only is the maximum amplitude of the P-wave in acute coronary artery closure of interest, but also it is instructive to follow the variations in size or shape which occur in a series of electrocardiograms of the same individual (Table I). It has been found that beginning often on the very day of onset of the acute coronary artery closure and continuing to about the third, fourth or fifth day thereafter, the P-wave has the largest amplitude, and that from about the sixth day on the P-wave returns to normal. These figures and those that follow must not be taken too literally, for in many of the cases tracings were taken not daily but rather every other day, and occasionally there were no records for the first few days of the illness.

The P-waves were larger at a time when there was clinical and electrocardiographic evidence of acute coronary artery closure with severe circulatory embarrassment. Table I shows the times of appearance of the increase in the size of the P-wave, of its recession to normal, of RS-T changes, T-wave inversions, and also the days on which proof was obtained of severe myocardial and circulatory failure (such as congestion in the lungs, cyanosis of finger tips or lips, liver enlargement, severe dyspnea or orthopnea). Systolic blood pressure below 100 mm. Hg, considerable precordial or chest pain, leucocytosis (10,000 white blood cells, or more), fever (100° F. or more), are also listed. The day on which the coronary artery accident occurred is tabulated as 1 and hence the Arabic numerals on the chart indicate time in days in relation to this first day.

The records seem to show that if severe circulatory failure is present, as indicated by cyanosis, congestion of the lungs, enlarged liver, etc., then the size of the P-wave will be found greater than that seen at the time when physical signs or laboratory tests show recovery from acute circulatory failure. In the table the first 16 cases are those that had P-waves of 2 mm. or more and every single one of these shows this relationship. In the remaining 24 cases (Nos. 17 to 40) circulatory failure was found 20 times,

TABLE I
P-WAVE CHANGES IN ACUTE CORONARY ARTERY OCCLUSION RELATED TO CLINICAL OBSERVATIONS*

CASE NO.	NAME	AGE	SEX		MAXIMUM SIZE P-WAVE IN MM.	LARGE P-WAVE	NORMAL P-WAVE	RS-T CHANGES	T CHANGES	LUNG CONGESTION		LUNGS CLEAR	LIVER LARGE	CYANOSIS	SEVERE DYSPNEA	LOW BLOOD PRESSURE	SEVERE PAIN	FEVER	LEUCOCYTOSIS	MISCELLANEOUS
			F	M						PHY. SIGNS	X-RAY									
1	J. Br.	56	✓		2.5	1-4	6	1-3	4-6	1	6	25		1	1	3, 4, 18	1	4, 15	1, 2	
2	E. Ca.	40	✓		2.5	3	5+	3-12	12	1	1			1	1, 4		1, 4	2-9	3	
3	E. Eb.	51	✓		2.0	1-3	11	1-3	11	1	1			1	1		1	1-20	1-17	
4	N. Fi.	53	✓		2.0	3-8	9-10		7	1				1	1		1	2	1, 23	
5	N. Fr.	52	✓		2.2	2.7**	8+		1+	1	1			1	1	4	1	2-19	1, 23	
6	D. Go.	52	✓		2.8	1-9	82	3-9	3-9	1				1	1		1	2-6	2	
7	C. Ha.	39	✓		2.0	3-5	9-40	3-8	3+	1				1	1-2, 3	4, 20, 28	1, 2, 3	2-8	1-17	
8	J. Ha.	50	✓		2.1	3-5	6+	3-5	6	1				1	1-2	5, 9, 12, 14	1, 2	19, 27, 29	1	
9	J. La.	51	✓		2.0	1-5	9	1-9	1-9	1				1	1		1	2-7		Pt. died
10	R. Mo.	49	✓		2.0	5-7				6				1	1	16	1	1	1-9	
11	B. Ro.	47	✓		2.0	4	8	4-8	8+						1		1	4-7	5, 46	
12	H. Ro.	58	✓		2.0	3-7	20+	3-10	3+	1	7-35			2	2, 3		2, 3	3, 35	3-41	
13	L. Ru.	43	✓		2.2	1-5	13-37	1-3	3+	1				1	1, 5	5-6	1, 5	2, 7, 39	1, 6, 38	
14	S. Sc.	47	✓		2.9	2-3	6	2-3	2	1	6		5	1	1	1	1	1-14	1, 3, 10	
15	D. Sh.	58	✓		2.0	1-7**	10, 46	1-7	5+	1	1			1	2	6	1	2, 7	1	
16	H. St.	57	✓		2.0	3	5	1-14	11	1	2		1	1	1, 3, 14	3-29	1, 3, 14	2-16	1-24	
17	J. Ba.	42	✓		1.3	1**	3	1	3+	1	2, 7	9	2	1	1, 2, 3	8	1, 2, 3	2-10	1-13	
18	M. Br.	46	✓		1.7	1-6		1+	3	1	2, 20			1	1-20	3-17	1-20	1-21	1-21	Pt. died
19	C. Co.	51	✓		1.0				5+	3	5	2	2		1		1	3-8	5, 7	
20	E. De.	78	✓		0.8				1+	1					1		1	2-7	1	

*The day on which the acute coronary artery occlusion occurred is considered the first day and is tabulated 1, the second day of illness 2, the third 3, etc.

**In these cases the change in the P-wave was a notching or double summit, not an increase in size.

TABLE I (CONTINUED)

CASE NO.	NAME	AGE	SEX		MAXIMAL SIZE P-WAVE IN MM.	LARGE P-WAVE	NORMAL P-WAVE	RS-T CHANGES	T CHANGES	LUNG CONGESTION		LUNGS CLEAR	LIVER LARGE	CYANOSIS LIPS FINGERS	SEVERE DYSPNEA	LOW BLOOD PRESSURE	SEVERE PAIN	FEVER	LEUCOCYTOSIS	MISCELLANEOUS
			F	M						PHY. SIGNS	X-RAY									
21	J. De.	45		✓	1.9	4-6**		3-9	12	1	4			1	1	5-20	1-4	2-8	1-7	
22	E. Fe.	41		✓	1.5	4-9	18	4-9	4+	1	3			1	1, 9, 16	18, 24, 26	1-4	1-4	2	
23	J. Fl.	45		✓	1.8	3-6	29	3-7	6+	3				1	1, 2, 3		3-11	3-17	3-20	
24	R. Ga.	64		✓	1.4	3-5	13	3-7	14+	3				1	1, 2, 3		3-8	3-20	2	
25	H. Gr.	40		✓	1.0			2	2					1	1		2-7	2-7	2	
26	J. Ha.	45		✓	1.6	3 **	4	2	3-4						1		2, 3, 4	2, 3, 4	2, 3, 4	
27	F. He.	69		✓	1.0			5-12	12	3	3				1		3-31	4, 6, 12	4, 6, 12	
28	J. Ho.	51		✓	0.9			3-8	4	2					1		2-23	2-7	2-7	
29	H. Ja.	43		✓	1.5				2+	3	3			3	1-43		3-60	3, 9, 10	3, 9, 10	
30	H. Kn.	43		✓	1.4	3	18	3-5	3	4	11			3	1		3, 5	3, 6	3, 6	
31	T. Ln.	45		✓	1.4	4	8+	2-8	11	3				1	1, 2, 17		3-19	3, 5, 13	3, 5, 13	
32	W. Ov.	58		✓	1.7	1-8	9+		10	1				1			-	5, 7	5, 7	Pulmonary Edema 1
33	M. Pr.	56		✓	1.8	3-9	10+	2-10	12	1	2-6				1		1-30	1, 3, 23	1, 3, 23	
34	J. Rh.	55		✓	1.4	2-7	11	2	6						1		2-24	2, 16	2, 16	
35	M. Ro.	43		✓	1.6			2+	2+					1			2, 5, 6	2, 4, 29	2, 4, 29	
36	C. R.	66		✓	1.5	1-2**	4-15	1-15	15	1					1		2-7	3-13	3-13	
37	W. Se.	66		✓	1.8			13	13						1		2, 26	1-12	1-12	
38	S. Tu.	35		✓	1.9	1-6	16+	2-6	3+					1	1		2-6	2, 5, 33	2, 5, 33	
39	L. We.	43		✓	1.9	3	7	3+	7		1			1	1		2-10	1-23	1-23	
40	J. Wo.	53		✓	1.2	2-9	9+							1	1			1, 2	1, 2	

and corresponding to this there were changes in the P-wave in 14 of these 20 cases. Hence all together there were 36 patients in whom circulatory failure was evident, and in 30 of these (83 per cent) P-wave changes were recorded.

It is interesting to review the six cases in which there was no change in the P-wave to correspond to the clinical finding of circulatory failure. In case No. 19 (C. Co.) only four records were taken; whereas the average for each patient for the entire series of 40 was nine. In case No. 27 (F. He.) there were no tracings for the first five days. Hence there remain 4 cases, i. e., No. 28 (J. Ho.), No. 29 (H. Ja.), No. 35 (M. Ro.), and No. 37 (W. Sc.) for which no explanation can be offered for the absence of change in the P-wave of the electrocardiogram.

The change in the size (or shape) of the P-wave was associated not only with clinical signs of acute coronary thrombosis but with the electrocardiographic signs as well. RS-T abnormalities occur immediately after an acute coronary artery closure and usually last for a few days. They recede about the time T-wave inversions appear. In this study 30 cases with striking RS-T deviations were found, and in 28 of these the P-wave was larger while these were present than during the period when T-wave inversions appeared.

The P-wave was largest in Lead II in practically all of our cases. The P-wave was also prominent in one other lead but to a smaller extent, so that the variation in this wave was evident in combinations of Leads I and II, or Leads II and III. Twenty times the P-wave was most prominent in Leads I and II and on 11 occasions in Leads II and III.

Further details of the electrocardiographic changes were as follows: Abnormal T-waves were present in all cases but two, and were the most common of all the changes found in these cases of acute coronary artery closure. RS-T intervals were abnormal in 30 patients; QRS waves alone in 16 patients; P-R intervals, i. e., prolongation of the auriculoventricular conduction 9 times; large Q-waves in Lead III 8 times. A left axis deviation (left ventricular preponderance) was observed 23 times, a right axis deviation (right ventricular preponderance) 3 times.

The average age of all our patients was fifty years. There was only one female in the entire series.

DISCUSSION

It is very surprising that there should have been no description of the P-wave in acute coronary artery occlusion. A cursory glance at the illustrations used by authors^{3, 4} who have made comprehensive reviews of the subject of acute coronary artery thrombosis will show numerous examples of high voltage P-waves.

The mechanism of production of the increase in size in the P-wave in these cases requires explanation. This increase may be due to change in position of the auricles or perhaps due to a transient enlargement of these

chambers. However, there was usually no change in axis deviation of the ventricles, nor in the size of the QRS complexes, and these are usually altered with change in heart position. Again, if rotation of the auricles occurred, one might expect an inversion of the P-wave as occurs, for example, in Lead III of the electrocardiogram in obese patients where the diaphragm is elevated.

There is a strong possibility that the enlarged P-wave represents auricular dilatation and perhaps hypertrophy. After closure of a coronary artery the auricle has a greater function to fulfill, since the ventricle is injured. This seems the more plausible when one recalls what happens in the heart of a dog after a coronary artery has been ligated. The involved area of the ventricle is practically paralyzed, it becomes cyanotic and dilated, the ventricular contractions are feeble.

Another explanation may be that increased intra-auricular pressure produces auricular dilatation. With the fall in systemic pressure a stasis may occur in the great veins of the neck, and the auricles, being in intimate pressure and volume relations with them, will sustain a rise in the intra-auricular pressure, and dilatation of these chambers will follow. Clinical experience supports this theory, for the large P-waves appear when there are signs of venous engorgement such as large tender livers, dilated cervical veins, congestive râles at the lung bases.

There were only eight patients among the forty in whom there were no changes in the size of the P-wave. Only a variation of at least 0.5 mm. was considered a change. Considering the limits of an investigation of this sort and considering that 32 cases out of 40 showed variations in size, and occasionally in the shape of the P-wave, and that these changes corresponded to and varied with the clinical (83 per cent) and electrocardiographic findings (93 per cent) that occur in acute coronary artery closures, it is felt that the P-wave abnormalities are a result of changes produced in the auricle or auricles by the acute coronary artery thrombosis. The left auricle is probably the chamber most frequently affected, since the left ventricle is most often injured. Perhaps this is the reason the P-wave changes occur more frequently in Leads I and II than in Leads II and III.

The P-wave changes have been found very helpful in making an electrocardiographic diagnosis of coronary artery occlusion. Very frequently, single equivocal tracings, as for example, one showing iso-electric (flat) T-wave in Lead I, will suggest a coronary artery accident if a big P-wave is present.

In the table the headings "large P" and "normal P" indicate that at first the P-wave is larger than normal and that when it becomes smaller it reaches its usual size. However, no direct proof has been adduced to show that the P-wave in the first few days of an acute coronary artery occlusion is larger than the individual's P-wave before the accident to his heart. Since, however, the P-waves of 2 mm. or more occurred in a much higher percentage than normally, it seems reasonable to believe that these are

abnormally large P-waves for these patients and that the subsequent smaller size of the P-waves is probably their normal size. Using the same reasoning on the 24 cases in which the P-wave was never 2 mm. in size, it seems logical to assume that this wave in the early days of illness is relatively large and that later when it becomes smaller it reaches the normal for the patient. In the table, then, the word "large" signifies either a relative increase in size of the P-wave or a relative and absolute increase, and the word "normal" refers to its subsequent smaller size.* In some five or six private cases in which electrocardiograms were available before the acute coronary artery thrombosis took place it was clearly apparent that the first P-waves were relatively or absolutely increased in size and the subsequent smaller waves were a return to normal size.

SUMMARY

In 40 cases of acute coronary artery occlusion definite changes in the P-waves occurred in 32 patients (80 per cent). These changes consisted for the most part in increase in amplitude of the P-wave of at least 0.5 mm. and occasionally in notching or widening of the auricular complex. In 16 patients (40 per cent) the P-waves measured 2 mm. or more in height in some lead.

The change occurred more frequently in Leads I and II rather than in Leads II and III, but always in Lead II. It is suggested that P-wave changes in Leads I and II are associated with left auricular dilatation.

The P-waves were larger in the first few days of acute illness when cyanosis, congestion of the lungs, enlarged liver, severe dyspnea or orthopnea were present, and became smaller when there was recovery from circulatory failure. The P-waves were larger when RS-T changes were present and returned to normal when T-wave inversions appeared.

There is evidence that the larger P-wave early in acute coronary artery disease is indicative of a dilated auricle, and it is suggested that this chamber takes over a portion of the work of the injured ventricle.

The increase in size or the change in shape of the P-wave is one of the electrocardiographic signs of acute coronary artery occlusion.

I am indebted to Dr. Harold E. B. Pardee for his interest in this study and for many valuable suggestions.

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*Strictly speaking the word "large" should be restricted to P-waves of 2 mm. or over, as it has been done in the body of this article, but not necessarily so in the table.

CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE

IV. MITRAL INSUFFICIENCY AND MITRAL STENOSIS*

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THE recent reports of experimental studies of the cardiodynamics of acute and of chronic mitral insufficiency^{1, 2} and of acute and of chronic mitral stenosis^{2, 3, 4} have made desirable a correlation of the clinical with the experimental findings in these valve lesions. With this objective this clinical study was made.

MITRAL INSUFFICIENCY

Dynamically, mitral insufficiency caused by rheumatic scarring has long been recognized as a benign lesion (Mackenzie). Experimental study of the effect of acute¹ and of chronic² mitral insufficiency in dogs has shown that the lesion is well tolerated, provided the insufficiency is not too great. From optical records taken of the pressure changes in the left auricle, left ventricle, aorta, and pulmonary artery in acute mitral insufficiency¹ it was shown that systolic and diastolic aortic pressures fall for two to four beats following the production of insufficiency, resulting in a diminution of the pulse pressure. After a brief period equilibrium was established at a reduced level and the pulse pressure was restored to normal, restoring the normal systolic discharge of the left ventricle. After the lesion was produced, auricular pressure rose and remained elevated at a constant level. It was concluded that the left ventricle quickly compensates for the lesion and thus restores a normal balance of the systolic discharges of the right and left ventricles. Little regurgitation was shown to occur during the isometric period, because of the briefness of this phase, and most of the leak takes place during ejection and in early diastole. As long as the cardiac muscle was efficient, no back pressure effect was felt by the right heart and the pressure in the pulmonary artery remained normal. The duration of the systolic phases was shown to be practically unaltered—once the lesion was stabilized. A very slight lengthening of the isometric period was noted in the first cycle following production of the lesion, the phase returning to normal or lengthening slightly immediately. The variation was never more than a few thousandths of a second. Immediately after insufficiency was produced the ejection period was slightly shortened and then was immediately restored to normal.

Clinical Observations.—Fifteen young patients with clinical evidence of mitral insufficiency were the subjects of this study. The diagnosis of mitral insufficiency was made on the following evidence: (1) history of rheumatic fever; (2) cardiac enlargement; (3) a blowing systolic murmur at the apex which is transmitted to the axilla replacing the first heart

*From the Medical Clinic and Electrocardiographic Laboratory of Mt. Sinai Hospital of Cleveland.

sound or following it; (4) orthodiagraphic evidence of mitral insufficiency—enlargement of the left ventricle and dilatation of the left auricle. In no instance was there clinical evidence of active infection or of failure, and the blood pressure was within normal limits. The method of study has been given in a previous report.⁶ Briefly, the measurements of the phases of the cardiac cycle were made clinically from simultaneous records of the heart sounds and of the subclavian pulse. Lead II of the electrocardiogram was recorded at the same time to check the cardiac mechanism. The heart sounds when recorded at the apex show the systolic and diastolic murmurs well, but the first and second heart sounds were often buried and could not be accurately used for purposes of measurement. When the stethoscopic attachment is moved away from the apex toward the midline the sounds are accurately recognized. In Table I the results of the average measurements of the phases of the cardiac systole are given. The previous diastole was measured in all instances. The cardiac mechanism was normal and was checked electrocardiographically. The isometric period varied from 0.017 to 0.065 sec. (average 0.032 sec.). In one case the lower figure (0.017 sec.) was slightly under the minimum normal as given by Wiggers and Clough⁵ and by Katz and Feil.⁶ In all other cases this phase was within normal limits but with a tendency to be nearer the lower figure.

The average ejection phase was normal, varying from 0.189 to 0.255 sec. Total systole (Col. 5) may be compared with the calculated systole ($S = 0.31 \sqrt{c}$, Col. 6). In all instances the calculated S exceeds ejection by 0.007 to 0.043 sec. (averaging 0.025 sec.) which is the usual difference in normal persons and represents protodiastole.

Summary.—Total systole and the chief phases of systole (isometric and ejection periods) were measured in fifteen patients with clinical evidence of mitral insufficiency of rheumatic origin. In all instances total systole

TABLE I
MITRAL INSUFFICIENCY

CASE	HEART RATE	ISOMETRIC PERIOD	EJECTION PERIOD	TOTAL SYSTOLE	CALCULATED SYSTOLE ($S = .31 \sqrt{c}$)	CALCULATED SYSTOLE MINUS EJECTION
J. M.	78	0.030 sec.	0.255 sec.	0.285 sec.	0.271 sec.	0.016 sec.
C. R.	78	0.031	0.232	0.263	0.270	0.038
P. V.	81	0.034	0.242	0.276	0.266	0.024
P. G.	86	0.048	0.237	0.285	0.258	0.021
A. S.	87	0.026	0.227	0.253	0.257	0.030
A. L.	88	0.027	0.232	0.259	0.255	0.023
M. H.	89	0.024	0.245	0.269	0.257	0.012
A. K.	90	0.040	0.208	0.248	0.251	0.043
D. S.	94	0.065	0.228	0.293	0.245	0.017
A. K.	95	0.047	0.208	0.255	0.246	0.038
T. J.	100	0.023	0.219	0.242	0.239	0.020
M. B.	104	0.033	0.201	0.234	0.235	0.034
C. B.	105	0.021	0.222	0.243	0.234	0.012
J. D.	109	0.018	0.189	0.207	0.230	0.041
R. S.	116	0.017	0.215	0.232	0.222	0.007

and the phases of systole were found to be within normal limits. When measured systole is compared with calculated systole, the normal difference is found to be present. These measurements are in agreement with experimental studies in this lesion as produced acutely by Wiggers and Feil.¹

MITRAL STENOSIS

This valve lesion has been produced experimentally by a number of investigators. Katz and Siegel³ studied the effects of acutely produced stenosis, and Powers, Pilcher and Bowie⁴ studied the effect of chronic stenosis. The various methods of production of the experimental lesion and the study of the dynamics have been reviewed by the latter authors. The results of the various experimental workers have varied. Those of Katz and Siegel who produced acute stenosis of the mitral valve confirmed the work of some of the earlier investigators. They found that the heart rate was slowed in some instances. Total systole, and with it ejection of both ventricles, was abbreviated equally in most of the experiments. Therefore it was concluded that this change was not due directly to the valve lesion but rather was due to the diminution in coronary flow because of the fall in aortic blood pressure. Further, left auricular pressure was elevated and with it an increase in the magnitude of left auricular contraction. The pressure maximum of the left ventricle was decreased, resulting in a fall in systolic, diastolic and pulse pressures in the aorta. Variable pressure effects were noted on the right side. Occasionally presystolic vibrations were seen on the curves recorded from the left ventricle. An increase in rate of filling of the left ventricle occurred as evidenced by the steeper gradient of the left ventricular pressure curve during diastasis. Powers, Pilcher and Bowie⁴ made observations on five dogs with experimentally produced chronic mitral stenosis. In four of these animals the cardiac output ranged from 104 c.c. to 230 c.c. per kilogram per minute which figures are within normal limits. The output of the fifth animal was distinctly elevated, being 323 c.c. per kilogram per minute. The basal pulse rate was increased in four instances and normal in the fifth. The blood pressure was elevated in only one case.

Clinical Observations.—Twenty-one patients with conclusive clinical signs of mitral stenosis were the subject of this study. Twelve patients had normal mechanism and nine patients had auricular fibrillation, all confirmed by electrocardiograms. In Table II is seen the duration of the phases of systole together with the heart rates which varied from 61 to 94. Both the isometric and ejection periods were within normal limits (isometric period 0.012 to 0.064 sec.), (ejection period 0.217 to 0.281 sec.). Total systole was normal (from 0.248 to 0.324 sec.). Calculated systole when compared with ejection showed the normal difference (i. e., 0.014 to 0.045 sec.) in all instances but one. This patient, No. 9, had a difference of 0.056 sec. slightly in excess of the others.* It may be concluded therefore

*Patient 9 had signs of early cardiac failure, and this fact was doubtless responsible for the shortening of ejection and of total systole.¹

TABLE II
MITRAL STENOSIS, NORMAL MECHANISM

CASE NO.	HEART RATE	ISOMETRIC PERIOD	EJECTION PERIOD	TOTAL SYSTOLE	CALCULATED SYSTOLE ($s = .31 \sqrt{c}$)	CALCULATED SYSTOLE MINUS EJECTION
5	61	0.043 sec.	0.281 sec.	0.324 sec.	0.305 sec.	0.024 sec.
9	67	0.012	0.236	0.248	0.292	0.056*
8	72	0.038	0.268	0.300	0.282	0.014
1	74	0.045	0.239	0.284	0.284	0.045
7	75	0.064	0.255	0.310	0.277	0.022
4	76	0.025	0.254	0.279	0.275	0.021
10	76	0.032	0.268	0.301	0.275	0.007
2	81	0.026	0.243	0.269	0.268	0.025
12	81	0.067	0.243	0.310	0.268	0.025
6	82	0.047	0.241	0.288	0.265	0.024
11	91	0.039	0.217	0.257	0.251	0.034
3	94	0.028	0.228	0.259	0.247	0.019

*Patient had evidence of greater reduction of cardiac reserve.

TABLE III
MITRAL STENOSIS, AURICULAR FIBRILLATION

CASE NO.	HEART RATE	ISOMETRIC PERIOD	EJECTION PERIOD	TOTAL SYSTOLE	CALCULATED SYSTOLE ($s = .31 \sqrt{c}$)	CALCULATED SYSTOLE MINUS EJECTION
15	55	0.069 sec.	0.261 sec.	0.330 sec.	0.322 sec.	0.061 sec.
14	69	0.056	0.198	0.254	0.290	0.092
12	76	0.119	0.190	0.309	0.275	0.085
11	90	0.044	0.200	0.244	0.253	0.053
10	93	0.061	0.181	0.242	0.248	0.067
9	94	0.093	0.173	0.266	0.247	0.074
8	96	0.069	0.182	0.251	0.245	0.063
5	111	0.036	0.194	0.233	0.228	0.034
2	151	0.047	0.128	0.175	0.195	0.067

that in clinical mitral stenosis with normal mechanism no variation occurs in the duration of the chief phases of systole or in total systole. Table III shows the findings in the nine patients who had in addition, auricular fibrillation, but who had no evidence of congestive circulatory failure. The heart rates varied from 55 to 151 and the blood pressure was within normal limits. The isometric period varied from 0.036 to 0.119 sec. with an average of 0.07 sec. and was therefore slightly lengthened. Ejection varied from 0.128 to 0.261 sec. Total systole varied from 0.175 to 0.330 sec. When the calculated systole is compared with ejection, it is noted that the difference between these two figures varied from 0.061 to 0.092 sec. (average 0.062 sec.). This is in excess of the normal difference (0.028 sec.) and represents the shortening of ejection and with it total systole (previously reported in patients with auricular fibrillation).⁶ This shortening is due to the lack of the auricular contribution to ventricular filling which results in a reduction in the initial volume and tension of the left ventricle.

DISCUSSION

Clinical mitral insufficiency, as is the case in the experimental acute lesion, does not appreciably alter the duration of the isometric and ejection phases of systole. Likewise total systole falls within normal limits. When the duration of ejection is subtracted from the calculated systole, the normal difference is found (protodiastole). Clinical mitral stenosis, with normal mechanism, likewise did not show any deviation from the normal except in one instance (Case 9) where some degree of failure was present. This isolated abbreviation of systole we attribute to the element of failure. These normal figures are in agreement with the findings in the acute experimental lesion where the slight abbreviation of systole was found to be due to the interference with coronary flow. When mitral stenosis was associated with auricular fibrillation, abbreviation of ejection and of total systole occurred. This we believe was due to the lack of synergic auricular contraction and the absence of the auricular contribution to ventricular filling. We may conclude that stenosis of the mitral valve alone does not alter the dynamics of left ventricular systole. To compensate for the narrowed opening auricular hypertrophy occurs and the initial volume and tension of the left ventricle are not lessened. This is in agreement with pathological findings in this valve lesion—an hypertrophied and dilated left auricle. In the clinic we find little or no reduction in the pulse volume in mitral stenosis unless cardiac failure or auricular fibrillation occurs.

SUMMARY

Patients with mitral valve lesions were studied by means of the Wiggers modification of the Frank capsule and the measurements of the chief phases of systole were compared with the duration of these phases calculated from the formula $S = .31 \sqrt{c}$ from which the following conclusions were drawn:

Mitral Insufficiency.—The duration of the isometric and ejection phases and of total systole were within normal limits with one exception.

Mitral Stenosis.—In eleven of the twelve cases with normal mechanism the phases of systole and of total systole were normal. In one instance with slight failure, ejection and total systole were abbreviated. In nine patients with auricular fibrillation but with no signs of failure the phases of systole and total systole were shortened. These clinical findings are in agreement with recent experimental data.

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HEART DISEASE IN GENERAL MEDICAL PRACTICE*

PRELIMINARY REPORT OF MORBIDITY SURVEY CONDUCTED BY THE NEW
YORK STATE DEPARTMENT OF HEALTH

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HEART disease is the leading cause of death in this country. In 1929 almost a quarter of a million deaths in the registration area of continental United States were ascribed to diseases of the heart—more than double the mortality from cancer, which was second in numerical importance.

The death rates of the forty-six registration states ranged from a minimum of 90 per 100,000 in Oklahoma to a maximum of 304 in Vermont. A rate below 100 was recorded in one other state—New Mexico, 92; twenty-five states had rates between 100 and 200 and eighteen states between 200 and 300 (Fig. 1).

Various factors are responsible for this great variation in the rates; one, the age composition of the population, is self-evident. Since the death rate from heart disease increases with age, a state with an old population, because of this fact alone, will have a higher death rate than a state with a young population. The weight of the age composition can be easily evaluated numerically—relating the death rates to the proportion of persons in the population who were more than forty-five years of age, we find the coefficient of this correlation to be most significant: $+0.832 \pm 0.031$.

In 1928, the latest year for which the information is available, heart disease was ninth in importance among the causes of death of children between one and ten years of age, pneumonia being first, followed in order by accidents, diarrhea and enteritis, diphtheria, influenza, tuberculosis, measles, and whooping cough. Between ten and fifteen years, heart disease was second, accidents being first. In the age group fifteen to twenty-four years, heart disease was fifth, accidents being first, followed by tuberculosis, pneumonia, and puerperal causes. Heart disease was third in the next age group, twenty-five to thirty-five years, tuberculosis leading, with accidents second. Between thirty-five and forty years, heart disease was second and tuberculosis first. At all ages after the fortieth year, heart disease held first place.

The percentage of deaths ascribed to heart disease in the registration states increased quite uniformly with age, with the exception of a singular peak at ten to fourteen years (Fig. 2). This relatively high mortality was not unique for 1928; the corresponding figures in the preceding years demonstrate the same fact. Between five and forty years, heart disease

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was relatively more important among females than males; in the age groups forty to forty-four years and "seventy-five years and over" the ratios for the sexes were the same, while in the other age groups the percentage was higher among males.

Although most of the deaths from heart disease occur at the farther end of life, the number of deaths in the younger ages is by no means small. In 1928, for example, the deaths of 30,675 persons under forty-five years

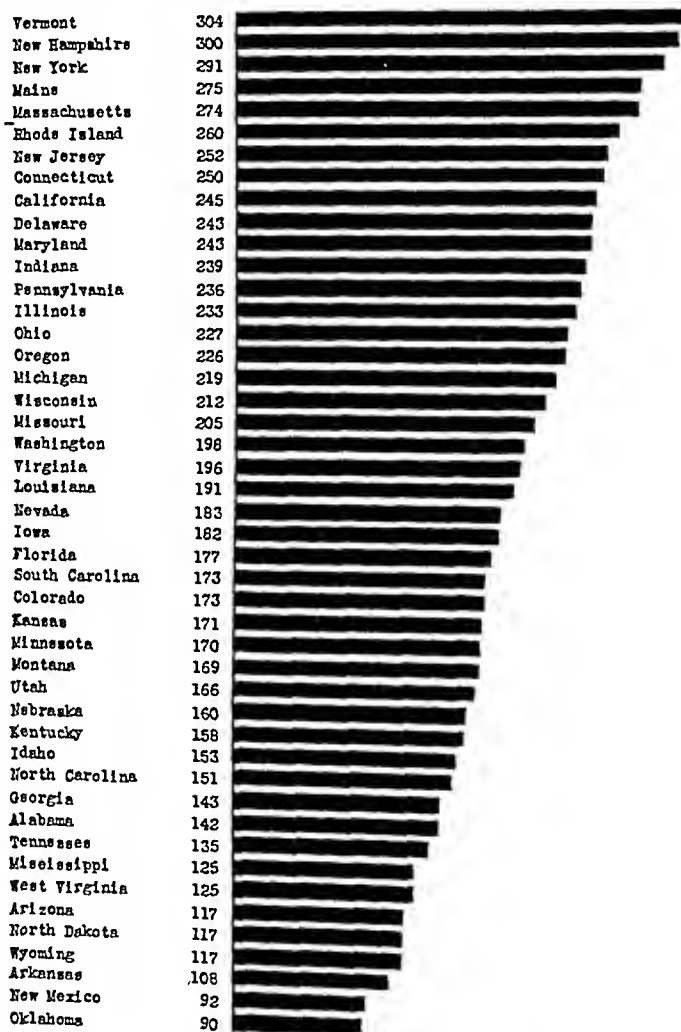


Fig. 1.—Death rates per 100,000 population, from heart disease, registration states, 1929.

of age were recorded in the entire registration area. This is a larger number than the deaths at all ages during that year from many important causes: typhoid fever (5,620), diabetes (21,747), diseases of the puerperal state (15,691).

Mortality From Heart Disease in New York State.—The six leading causes of death in the state of New York in 1930 were: heart disease (277 per 100,000 population); cancer, all forms (123); pneumonia, all forms (102); accidents (81); acute and chronic nephritis (77); and tuberculosis, all forms (71).

In 1900, heart disease, with a rate of 133, was fourth among the causes of death, being preceded by tuberculosis (217), pneumonia (217), and diarrhea and enteritis, all ages (148), (Fig. 3).

In the course of thirty years the death rate from heart disease more

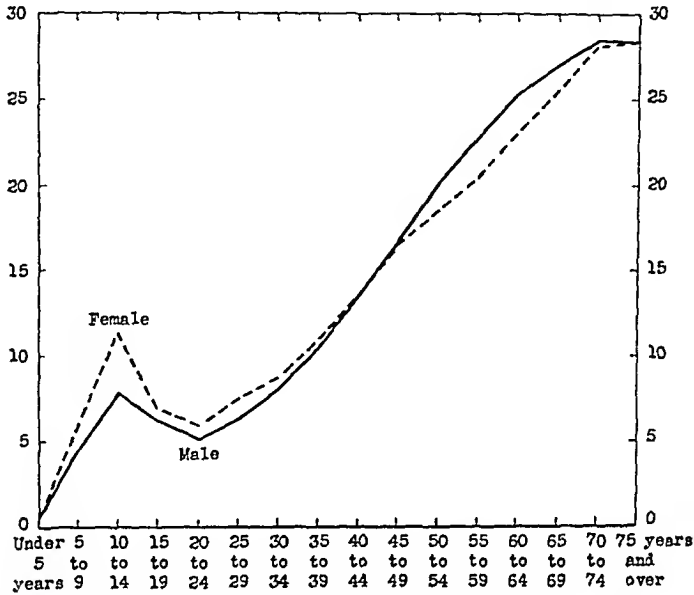


Fig. 2.—Deaths from heart disease per 100 deaths from all causes, by sex and age, registration states, 1928.

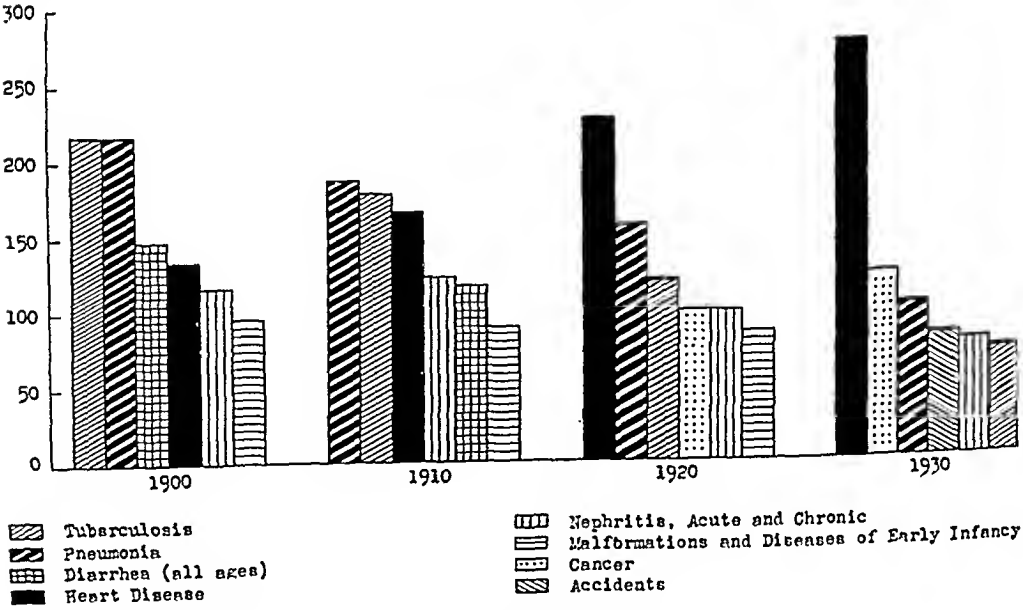


Fig. 3.—Death rates per 100,000 population, from leading causes, New York state, 1900, 1910, 1920, 1930.

than doubled, while mortality from the other causes either rose by a smaller increment (cancer from 67 to 123, or 84 per cent; accidents from 78 to 81) or decreased (Fig. 4).

The mortality from heart disease has been mounting steadily since the beginning of the century with the exception of 1905, 1908, 1919, 1927, and

1930. The recession of the death rate in 1927 may be explained by the fact that the high rate of 1926 was a direct consequence of unusually severe weather in February, March, and April of that year. In 1919, as a sequel to the influenza epidemic, the contingent of sufferers from heart disease was considerably reduced; the drop in the rate in 1905, 1908, and 1930 similarly followed the uncommon prevalence of influenza and pneumonia in the immediately preceding years: 1904, 1907, and 1929. The death rate from heart disease in the latter year was the highest ever recorded in the state—the January rate (421.7) establishing the present maximum for any month. The direct bearing of influenza and respiratory diseases on the mortality from heart disease was demonstrated by an analysis of the death certificates for the state, outside of New York City, for January, 1929. Of the 2,345 deaths attributed to heart disease as a primary cause, 247 were complicated with influenza, 179 with broncho-

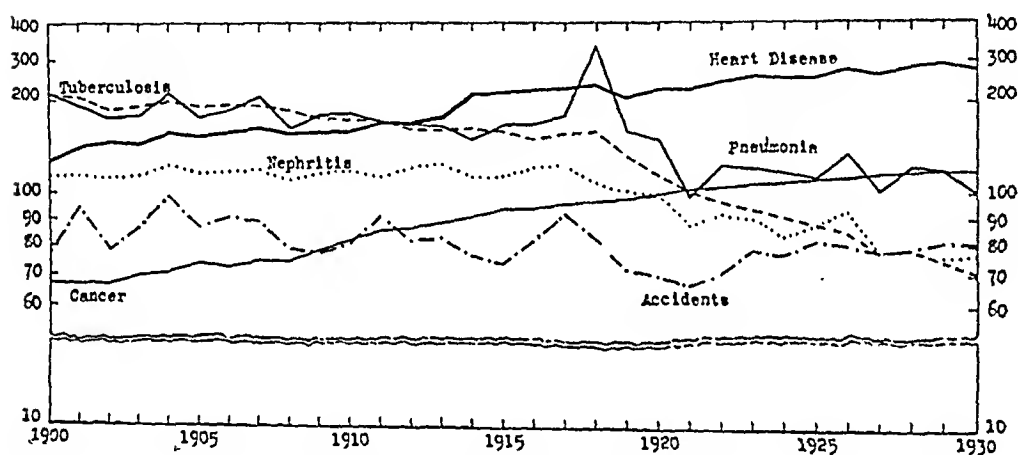


Fig. 4.—Death rates per 100,000 population, from heart disease and other important causes, New York state, 1900-1930.

pneumonia, and 265 with other respiratory diseases—a total of 691 with influenza and other respiratory complications; in January, 1928, the corresponding number was 190. The excess of 501 represents almost two-thirds of the difference in the January deaths in these two years.

Plan and Scope of Heart Survey.—Quantitative studies carried out in recent years indicate that from 2 to 4 per cent of the people are afflicted with heart disease. A survey of sickness¹ was conducted by the New York State Department of Health in 1927, in which more than one hundred physicians, serving a population of one hundred thousand, reported each week cases of various types of disease in their practice. Cases of heart disease totalled 4,123—a larger number than of all reportable communicable diseases, 3,212. In a more intensive survey of a single county, Essex,² cases of heart disease totalled 535, while the entire reportable group was represented by only 312 cases.

The next step is, of course, from the general to the particular—from an evaluation of the size of the problem to a study of details. The state-

ment that from four to eight million people in this country, including a large number of children and young adults, suffer from heart disease, is naturally followed by the query: What is to be done about it? Experts tell us that "from the point of view of prevention and relief" it is essential to realize the complex nature of heart disease and here "from practically every point of view, information is inadequate."³

Certain clinics and hospitals have done a great deal of good work in an-

SURVEY OF MORBIDITY FROM DISEASES OF THE HEART

Confidential report by..... M. D. Date.....
 P. O.

Name of patient..... Age..... Sex..... Color.....
 Single..... Married..... Widowed..... Divorced..... Country of birth..... Occupation.....
 Have others in family heart disease? Yes..... No..... Unknown..... If so, what was their age when disease was discovered.....

Etiology

1 Rheumatic fever.....	5 Congenital.....
Date of first attack.....	6 Chronic high blood pressure.....
2 Chorea.....	7 Thyrotoxicosis.....
3 Syphilis.....	8 Other causes (specify).....
Date of chancre.....	
4 Other infection (specify organism).....	9 Etiology unknown.....
State nature of infection (diphtheria, etc.).....	10 Nervous heart.....

Pathology

1 Pericardial disease: (a) Inflammation.....	(b) Effusion.....
2 Damage to valves, state valve affected.....	
3 Aortitis.....	Aneurism.....
4 Damage to coronary vessels.....	
5 Damage to myocardium.....	

Course of patient's disability
 State date or age of patient at beginning of:

(a) Cardiac symptoms.....
(b) Occasional rest in bed.....
(c) When patient first became bedridden.....
(d) When patient became permanently bedridden.....

Type of treatment

1 Removal of foci of infection: (a) Tonsillectomy.....	(b) Other foci (specify).....
2 Anti-luetic treatment.....	
3 For hypertension.....	
4 Cardiac treatment: (a) By drugs.....	(b) By rest.....
5 Other treatment.....	

Remarks: (Use reverse side if necessary)

Fig. 5.

alyzing and making public their experiences with cardiac patients, but here it is the more advanced stages of heart disease that are dealt with. It is the general practitioner who sees the early symptoms; his observations are certainly as worthy of study and may produce as valuable results as the more detached conclusions of specialists. Since cases of heart disease are not reportable, facts from private practice can be collected only with the voluntary cooperation of physicians. That such cooperation may be secured was demonstrated by the two surveys of general morbidity

mentioned earlier. A proposal for a survey of morbidity from heart disease to be conducted by the New York State Department of Health, outlined before the American Heart Association, received the endorsement of the Association as well as of the State Medical Society.⁴

The survey commenced in January, 1931, and during the first six months of the year reports were received from 186 physicians practicing in urban and 110 in rural communities—a total of 296.

The purpose of the general questions in the report form (Fig. 5), as well as those relating to etiology, pathology, and type of treatment, needs no elaboration. The section relating to the course of the patient's disability was inserted with the hope that if the answers are sufficiently numerous and complete it may be possible to make a mathematical determination of the important stages in the life of a cardiac patient.

GENERAL RESULTS

This paper will be limited to a provisional analysis of the 1,934 cases reported in January to June, 1931. No reference will be made to the course of the patient's disability or to the type of treatment employed. It is hoped to discuss these facts, as well as details of the other items, in a subsequent study.

Sex and Conjugal Condition.—The distribution of the cardiac cases according to the sex and conjugal condition of patient is shown in Table I.

TABLE I

MARITAL CONDITION	TOTAL	MALE	FEMALE
Total	1,934	933	1,001
Single	453	227	226
Married	1,062	555	507
Widowed	362	125	237
Divorced	15	4	11
Unknown or not stated	42	22	20

There is no special significance in the excess of married men and widowed women; this is very likely a reflection of the relative size of these classes in the general population. According to the census of 1930, there were in the State of New York 2,761,908 married men and 2,738,973 married women.* Similarly, the number of widows, 522,983, was more than double the number of widowers, 197,157.

Color and Nativity.—The majority of the 1,934 patients were white, the colored numbering only 27 (negroes, 22; other colored, 5). Among the white, the number of native-born (1,504) was six times that of the foreign-born (255).

*This apparent paradox undoubtedly results from the fact that at the time the census was taken the wives of a number of foreign-born men resided abroad.

TABLE II

COLOR AND NATIVITY	TOTAL	MALE	FEMALE
Total	1,934	933	1,001
White	1,907	919	988
United States	1,504	719	785
Total foreign	255	131	124
Austria	3	2	1
Canada	29	18	11
Denmark, Norway, Sweden	7	3	4
England, Scotland, Wales	25	14	11
Germany	39	18	21
Hungary	2	—	2
Ireland	32	17	15
Italy	48	22	26
Poland	46	25	21
Russia	11	5	6
Other foreign countries	13	7	6
Country not stated	148	69	79
Colored	27	14	13
Negro	22	10	12
Other colored	5	4	1

Occupation.—Of the 933 males, the occupation of 43 was not stated; of the remainder, 90 were under twenty years, practically all of whom had no stated occupation. The percentage distribution of the remaining 800 over twenty years of age was as follows:

Total	100.0
No occupation	19.6
Farmers	13.4
Unskilled laborers	11.0
Skilled laborers	10.0
Merchants, retail dealers, "business men"	7.0
Clergymen, physicians, lawyers, teachers, members of other professions	6.1
Clerical workers	6.1
Factory operators	4.3
Salesmen, including retail clerks	2.5
Chauffeurs, truck drivers, delivery men	2.0
Railroad workers	1.9
Insurance and real estate agents	1.7
Caretakers, watchmen, janitors	1.6
Gardeners	1.3
Factory owners, managers, officials	1.3
Foremen	1.3
Other occupations	8.9

The occupation of 28 of the 1,001 females was not stated. Deducting those under twenty years, practically all of whom had no stated occupation, we have 868, regarding whose occupation some definite statement was entered. The percentage distribution by occupation was as follows:

Total	100.0
No occupation	12.8
Housewives	70.2
Teachers	3.0
Clerical workers	2.9
Nurses	2.9
Domestic and personal service	2.8
Factory operators	1.0
Other occupations	4.4

Most of the persons without occupation were over sixty years: 103 of the 157 males and 84 of the 109 females.

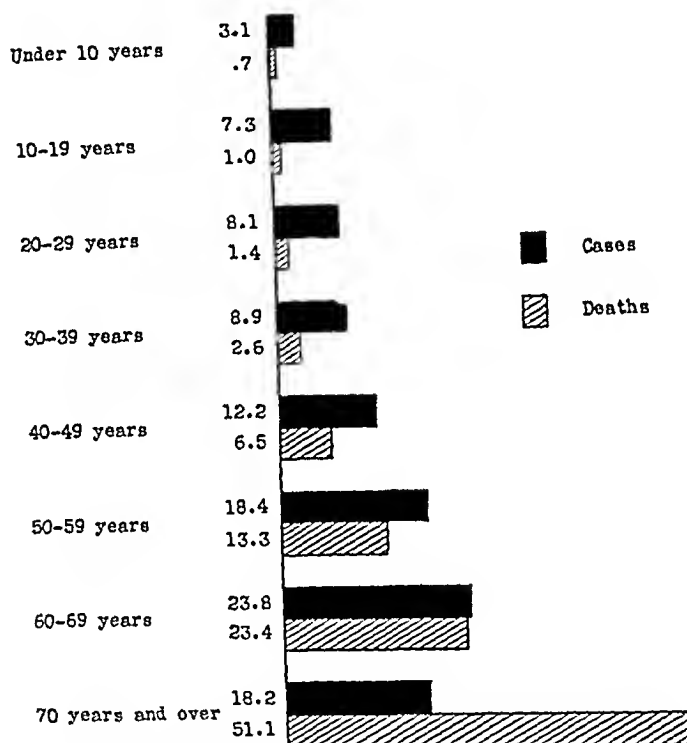


Fig. 6.—Percentage distribution by age of patients in heart survey and of deaths from heart disease in upstate New York, 1930.

Age.—In Table III is shown the distribution of 926 males and 992 females according to age (the ages of 7 male and 9 female patients were not given); and in Fig. 6 the percentage distribution of all deaths from heart disease in upstate New York in 1930.

The curves of cases for both males and females have a low point in the youngest age group, rising to a maximum at sixty to sixty-nine years and declining in the oldest group "seventy years and over."

The percentages of morbidity and mortality are strikingly different except in the age group sixty to sixty-nine years in which they are practically the same: 26.0 per cent of the males being in this group, in which occurred 25.1 per cent of the deaths; among the females, the corresponding percentages are 22.1 and 21.4. Under forty years is found one-quarter of all male cases as compared with 5.5 per cent of the deaths; among

females, 29.9 per cent of the cases and 5.8 per cent of the deaths. In the oldest group "seventy years and over" fall one-fifth of the patients and almost one-half, 47.4, of the total male deaths; among females, 16.8 per cent of the cases and 55.3 per cent of the deaths.

TABLE III

AGE	TOTAL		MALE		FEMALE	
	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS
Total	100.0	100.0	100.0	100.0	100.0	100.0
Under 10 years	3.2	0.7	3.1	0.7	3.3	0.6
10-19 years	7.2	1.0	7.1	1.0	7.3	1.1
20-29 years	8.1	1.4	7.0	1.3	9.1	1.5
30-39 years	8.9	2.6	7.5	2.5	10.2	2.6
40-49 years	12.0	6.5	9.8	7.2	14.1	5.8
50-59 years	18.5	13.3	20.0	14.8	17.1	11.7
60-69 years	24.0	23.4	26.0	25.1	22.1	21.4
70 years and over	18.1	51.1	19.5	47.4	16.8	55.3
Average age	51.5	67.6	52.9	66.7	50.3	68.7
Median age	55.7	70.3	57.7	69.0	53.5	71.7

The average age of all patients was 51.5 years; males, 52.9 and females, 50.3; the corresponding median ages were 55.7, 57.7, and 53.5. The average ages at death from heart disease in 1930 were 67.6 for both sexes, 66.7 for males and 68.7 for females; the corresponding median ages were: 70.3, 69.0, and 71.7.

ETIOLOGY

The etiology was indicated in practically all of the reports; the distribution of the important types by sex is shown in Table IV.

TABLE IV

ETIOLOGY	NUMBER			PER CENT		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
Total	1,872	907	965	100.0	100.0	100.0
Congenital	45	23	22	2.4	2.5	2.3
Rheumatic infections	511	221	290	27.2	24.3	30.0
Syphilis	86	65	21	4.6	7.2	2.2
Other acute infections	272	127	145	14.5	14.0	15.0
Arteriosclerosis	164	90	74	8.8	9.9	7.7
Hypertension	376	161	215	20.1	17.8	22.3
Thyrotoxicosis	67	11	56	3.6	1.2	5.8
Other factors	134	74	60	7.2	8.2	6.2
Unknown	217	135	82	11.6	14.9	8.5

N. B. Rheumatic infections comprise: rheumatic fever, 409; tonsillitis, 75; chorea, 27; other infections: streptococcus (mainly scarlet fever), 57; teeth, 43; influenza, 42; pneumonia, 32; diphtheria, 23; typhoid fever, 14; unclassified, 61.

In 27.2 per cent of the cases, rheumatic infection was given as the etiological factor. Hypertension was next, 20.1 per cent; other acute infections, 14.5 per cent; arteriosclerosis, 8.8 per cent; syphilis, 4.6 per cent; thyrotoxicosis, 3.6 per cent; congenital, 2.4 per cent. The etiology of 11.6 per cent of the cases was unknown (Fig. 7).

The proportion of syphilitic heart disease among males was more than three times that among females, and there was also a greater prevalence, though not to the same degree, of the arteriosclerotic heart. Rheumatic heart was more prevalent among women.

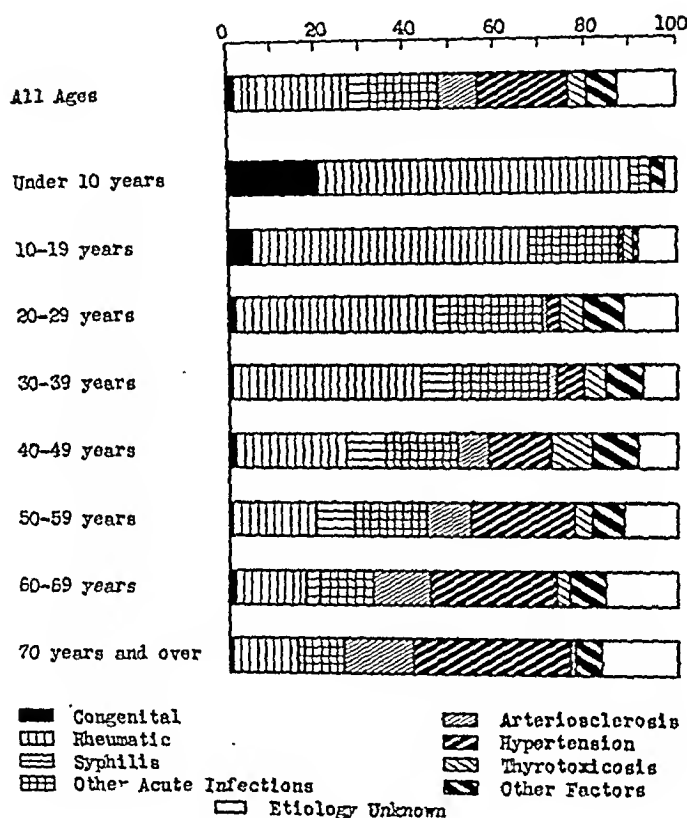


Fig. 7.—Percentage distribution of cases in heart survey by age and etiology.

The leading etiological factor under twenty years was rheumatic infection, 64 per cent; other acute infections being second, 15 per cent; and congenital third, 10 per cent. Rheumatic infection held first place in the next age group twenty to forty years, 44 per cent; followed by other acute infections, 21 per cent; and etiology unknown, 9 per cent. At forty to sixty years, arteriosclerosis combined with hypertension was in first place, 28 per cent; rheumatic infection second, 21 per cent; and other infections third, 16 per cent. After the sixtieth year, arteriosclerosis and hypertension were indicated in 46 per cent; rheumatic infection in 16; and unknown etiology in 15 per cent. Age forty years is frequently taken as a dividing line for the leading etiological types of heart disease. Their

percentage distribution under forty and over forty, as well as the median ages, are shown in Table V.

TABLE V

ETIOLOGY	UNDER 40 YEARS	OVER 40 YEARS	MEDIAN AGE
Total	27.4	72.6	55.7
Congenital	55.6	44.4	30.0
Rheumatic infections	52.1	47.9	38.6
Syphilis	20.0	80.0	51.6
Other acute infections	35.8	64.2	51.8
Arteriosclerosis	3.1	96.9	65.0
Hypertension	4.0	96.0	64.8
Thyrotoxicosis	27.3	72.7	47.1
Other factors	22.6	77.4	55.6
Unknown	18.1	81.9	62.0

Cases of rheumatic heart were only slightly more numerous among the younger patients. Syphilitic heart was four times more prevalent after forty years, while practically all cases of arteriosclerosis and hypertension fell in the older group. Cases of unknown etiology, contrary to the findings in some clinical studies, were largely represented in the older group.

PATHOLOGY

A definite statement of pathological changes was made in 1,826 cases. The distribution according to sex is shown in Table VI.

Damage to valves represented about one-half of the specified types; the proportion being markedly greater in females than males. In practically

TABLE VI

PATHOLOGY	NUMBER			PER CENT		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
Total	1,826	893	933	100.0	100.0	100.0
Damage to valves	888	402	486	48.7	45.0	52.1
Mitral	693	306	387			
Aortic	51	24	27			
Tricuspid	6	3	3			
Mitral and aortic	96	52	44			
Mitral and tricuspid	4	3	1			
All valves	14	7	7			
Valve not stated	24	7	17			
Damage to myocardium	528	248	280	28.9	27.8	30.0
Damage to coronary vessels	361	212	149	19.8	23.7	16.0
Aortitis	28	14	14	1.5	1.6	1.5
Aneurysm	13	10	3	0.7	1.1	0.3
Pericarditis	8	7	1	0.4	0.8	0.1

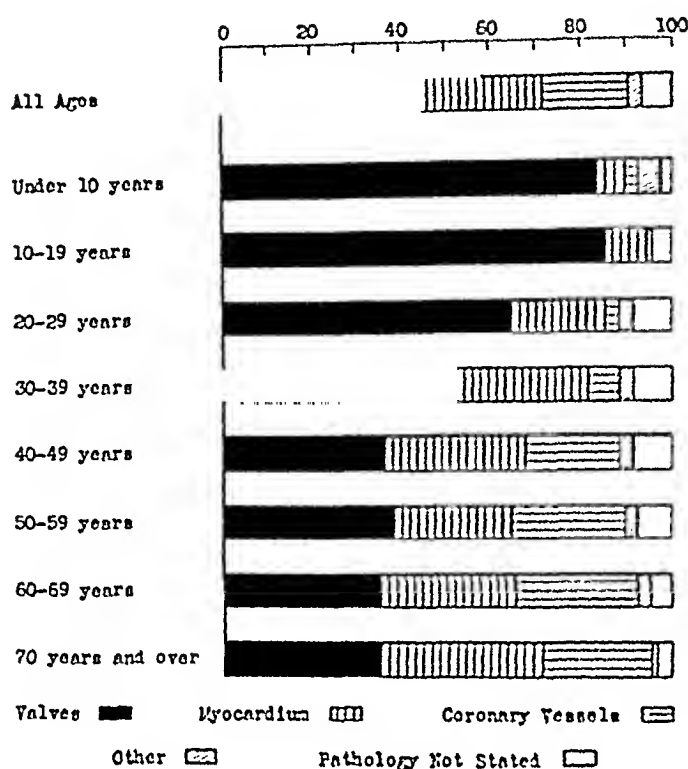


Fig. 8.—Percentage distribution of cases in heart survey by age and pathology.

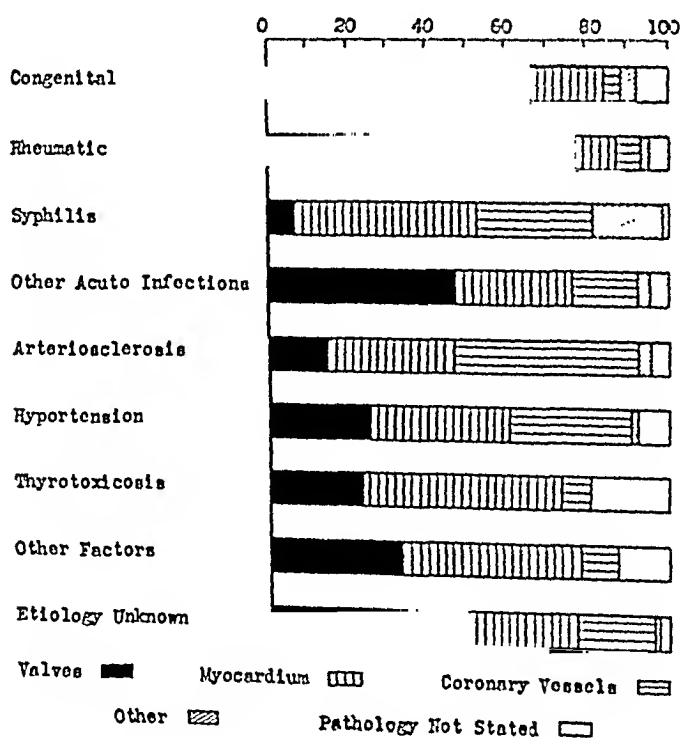


Fig. 9.—Percentage distribution of cases in heart survey by etiology and pathology.

all, the mitral valve was involved, either alone or in combination with others.

The prevalence of valvular defects was inversely related to age. Of the 193 patients under twenty years, 171, or 88.6 per cent, were said to have valvular disease. In the next age group, twenty to forty years, the percentage was 63.9 and after the fortieth year, 39.5. On the other hand, damage to the myocardium and coronary vessels increased with age. The former was present in only 8.3 per cent of the cardiac defects of the patients under twenty years, 27.4 per cent at twenty to forty years, and 30.2 per cent after forty years; the latter, in only 1 per cent of those under twenty years, 5.4 per cent in those twenty to forty years, and 25.7 per cent after forty years (Fig. 8).

The percentage distribution of the three important types of pathological changes among patients under forty and over forty years and the median ages for each type are shown in Table VII.

TABLE VII

PATHOLOGY	UNDER	OVER	MEDIAN AGE
	40 YEARS	40 YEARS	
Total	27.4	72.6	55.7
Damage to valves	40.9	59.1	49.2
Damage to myocardium	18.8	81.2	60.2
Damage to coronary vessels	5.1	94.9	62.1

Table VIII shows the percentage distribution of the leading etiological types according to pathology. Damage to valves was the major pathological change in congenital heart conditions, also where the etiology was said to be rheumatic infection, "other acute infection" or unknown. Damage to the myocardium was indicated in one-half of the cases with

TABLE VIII

ETIOLOGY	PATHOLOGY					
	TOTAL	DAMAGE TO VALVES	DAMAGE TO MYO- CARDIUM	DAMAGE TO CORONARY VESSELS	OTHER	NOT STATED
Congenital	100	67	18	4	4	7
Rheumatic infections	100	78	10	6	2	4
Syphilis	100	7	46	29	17	1
Other acute infections	100	48	29	16	3	4
Arteriosclerosis	100	15	32	46	3	4
Hypertension	100	26	35	30	2	7
Thyrototoxicosis	100	24	50	7	—	19
Other factors	100	34	45	9	—	12
Unknown	100	50	28	19	1	2

thyrotoxicosis as the etiological factor and almost an equal proportion of the syphilitic cases. Damage to the coronary vessels was of prime importance in the arteriosclerotic and only of lesser importance in the hypertensive type (Fig. 9).

SUMMARY

In January, 1931, the New York State Department of Health commenced a survey of morbidity from heart disease in the state, exclusive of New York City.

During the first half of the year 296 physicians reported 1,934 cases: 933 males and 1,001 females.

Age.—The distribution of the patients by age was as follows: under 40 years, 27.4 per cent; between 40 and 60 years, 30.5; 60 years and over, 42.1. The average age was 51.5 and the median age, 55.7 years.

The males were, as a group, younger than the females. Of the former, 24.7 per cent were under 40 years; of the latter, 29.9 per cent. The average age of the males was 52.9 years, the median age, 57.7; the average age of the females, 50.3 years and the median age, 53.5.

Etiology.—The leading etiological factors were: rheumatic infection, 27.2 per cent; hypertension, 20.1; arteriosclerosis, 8.8; syphilis, 4.6; congenital, 2.4; and in 11.6 per cent the etiology was unknown.

The proportion of syphilitic heart disease among males was three times that among females.

Pathology.—Damage to valves was indicated in 48.7 per cent; damage to myocardium, 28.9; to coronary vessels, 19.8.

Coronary disease was more prevalent among males, while valvular disease and damage to myocardium were more prevalent among females. The proportions were: coronary disease—males 23.7 per cent, females 16.0; valvular disease—males 45.0, females 52.1; damage to myocardium—males 27.8, females 30.0.

It is a pleasure to express my thanks to the physicians whose altruistic cooperation made this study possible. I am under obligation to Dr. Robert H. Halsey of New York City for valuable counsel at all stages of the survey. The report form was drawn up with the kind advice of Drs. A. E. Cohn, J. Hamilton Crawford, Herman O. Mosenthal, New York City; Richard C. Cabot and Paul D. White, Boston. For painstaking preparation of the raw material for statistical analysis, I am especially indebted to Miss Elizabeth Parkhurst, Research Statistician of the New York State Department of Health.

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REVERSAL IN DIRECTION OF THE QRS COMPLEX OF EXPERIMENTAL RIGHT BUNDLE-BRANCH BLOCK WITH CHANGE IN THE HEART'S POSITION*†

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CHICAGO, ILL.

IN A previous report¹ we have shown that the electrocardiographic appearance of ventricular extrasystoles elicited experimentally from fixed points is modified by the position of the heart. Rotation of the heart on its own long axis had the most marked influence. In fact, a change in the heart's position often reversed the direction of the QRS complex of the extrasystole in one or more leads. It was concluded from this study that the localization of the origin of the ventricular extrasystoles on the basis of the direction of QRS in Leads I and III was hazardous, especially in abnormal hearts. It was inferred by analogy that it was unsafe to attempt to locate the site of bundle-branch block from the direction of QRS in the various leads. In the present research, an attempt has been made to verify this inference with experimental bundle-branch block by determining the influence on the electrocardiogram of shifting the heart's position. This has been carried out successfully in four animals, in three of which the shift to successive positions was performed twice.

PROCEDURE

Each dog, anesthetized with barbital, had chest open and artificial respiration. The right bundle was cut in the intraventricular septum close to the A-V junction with a sharp knife thrust through the right ventricular wall, the procedure being essentially like the method most recently described by Roberts, et al.² The success of the cut in producing bundle-branch block was decided by the change in the electrocardiogram following the cut. A decided change in contour of the record with prolongation of QRS duration was taken to show the presence of block. This was verified postmortem by the location of the cut. Once the block was produced, the position of the heart was altered in the same manner and in the same order as in our extrasystole experiments (see previous report¹). An electrocardiogram was taken with the ordinary leads in each position of the heart, and at the end of each series with the heart placed in its original position to determine what change in configuration, if any, had developed.

*From the Cardiovascular Laboratory, Department of Physiology, Michael Reese Hospital and the University of Chicago.

†Aided by the Emil and Fanny Wedeles Fund for the study of diseases of the heart and circulation.

RESULTS

No attempt was made to quantitate the change in the electrical axis in the plane of the leads. A complete set of curves of one series of positions in Experiment A 12 is shown in Figs. 1 and 2.

The four segments of Fig. 1 show the change in appearance of the electrocardiogram as the heart's apex was elevated on the transverse axis at the base. The most noticeable change to be seen is the increase in

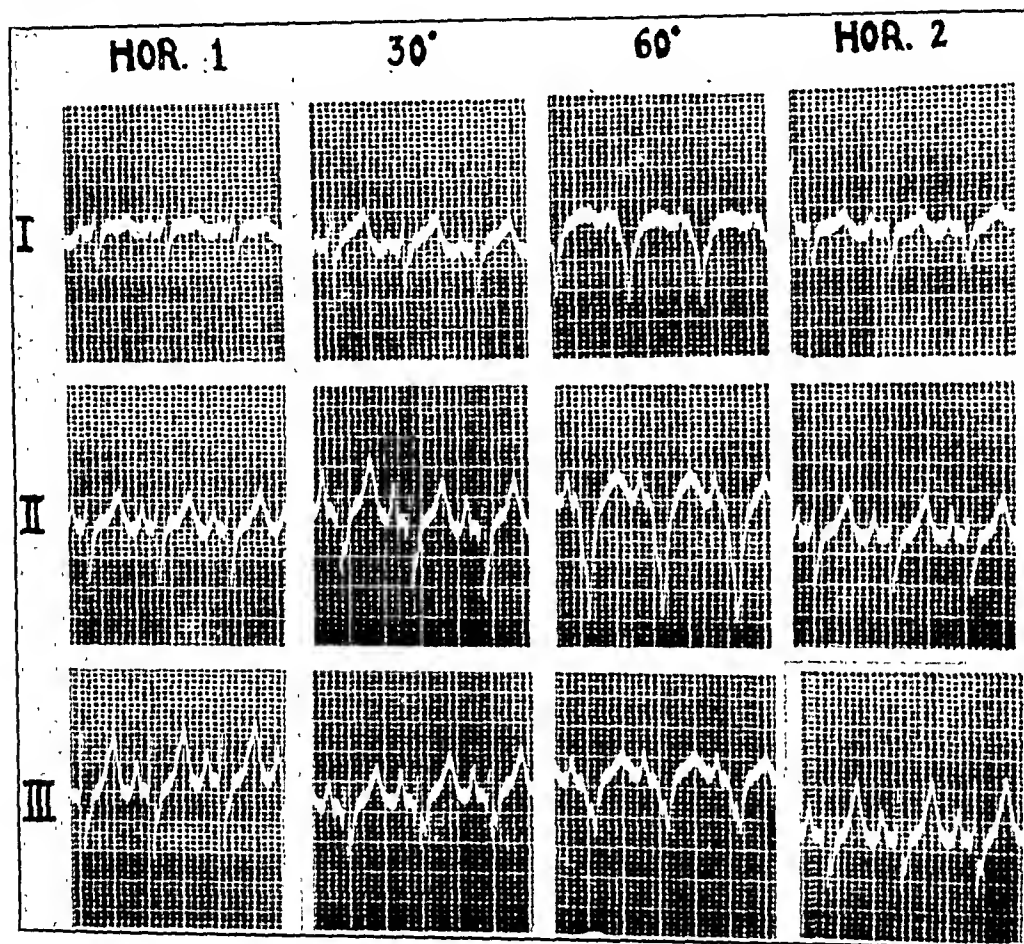


Fig. 1.

Figs. 1 and 2.—Segments of the three leads of the electrocardiograms taken in one of the two series of positions of Dog A12. The positions of the heart are: Hor. 1, heart horizontal and apex pointing caudad at start of series of positions; 30° and 60°, heart up to form, respectively, an angle of 30° and 60° with the long axis of the body, heart's apex pointing caudad; Hor. 2, position similar to Hor. 1, taken at end of series; RVA, heart's apex up 30°, to the right 15° of the long axis of the body, and heart rotated on its own long axis to bring right ventricle more anteriorly. LVA, heart's apex up 30°, to the left 15° of the long axis of the body, and heart rotated on its own long axis to bring the left ventricle more anteriorly. Note complete reversal of QRS_r and QRS_s in last two positions.

duration of the QRS straddle as the heart's apex points more and more anteriorly (compare Hor. 1, 30° and 60° of Fig. 1). The fourth segment of Fig. 1 (Hor. 2) shows the appearance of the electrocardiogram when the heart is returned to its original position after being placed in the whole series of positions shown in the other seven segments of Figs. 1

and 2. The electrocardiogram at the end is essentially the same as that taken at the start with the heart in this position (compare Hor. 1 and Hor. 2 of Fig. 1). This constancy of the electrocardiogram in the same position excludes the possibility that the changes in other positions of the heart might be due to an alteration in the character of the block. Any modifications that do occur therefore must be ascribed to the altered position of the heart. A similar check occurred in the other two animals

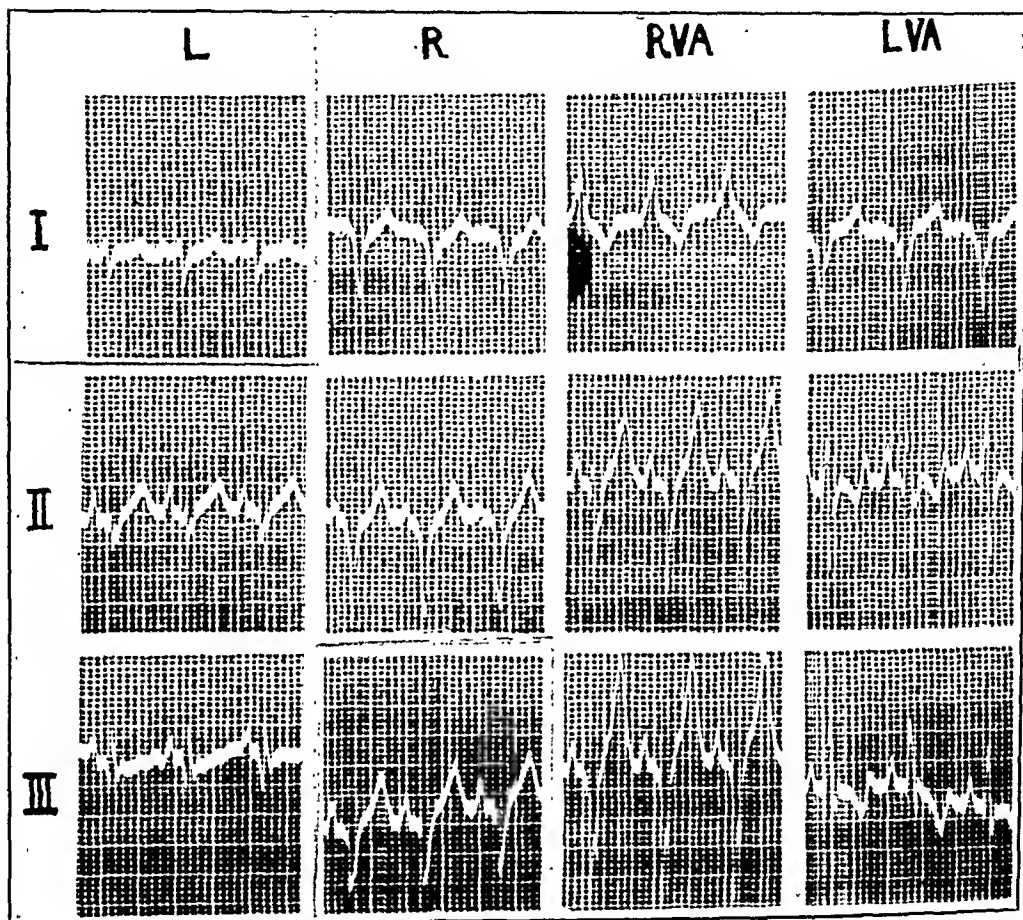


Fig. 2.—See legend under Fig. 1.

in which a curve was taken when the heart had returned to its original position.

It was found that the electrocardiographic deflections of the bundle-branch block were smaller when the heart's apex was to the left of the long axis of the body, without rotation of the heart on its own long axis, than when the apex was to the right of the long axis of the body. In three of the seven experiments the direction of QRS was reversed in Lead III when the heart was moved from one to the other position, viz., the inverted QRS in Lead III became upright on the shift from right to left. Fig. 1 shows a change in Lead III which is a step toward reversal. In one experiment a similar tendency occurred in Lead I in a reverse direction.

Without fail in the seven experiments, a complete reversal of QRS in Leads I or III was obtained when the heart was rotated on its own long axis from a position where the right ventricle was more anterior than normal to one where the left ventricle was more anterior than normal. The angle of rotation between the two positions was about 50° . In three of the experiments a reversal occurred in both Leads I and III, viz., in Figs. 2 and 3 (compare RVA and LVA) it will be seen that the QRS which was up in Lead I and down in Lead III in the first of these positions (RVA), became inverted in Lead I and up in Lead III in the other (LVA).

DISCUSSION

According to the classical viewpoint the curve shown in segment RVA of Figs. 2 and 3 would be classed as a right bundle-branch block, and the curve shown in segment LVA of Figs. 2 and 3 as left bundle-branch block; the terminology introduced by Wilson² would reverse the location. Yet the lesion in the heart was constant and was located in the right bundle-branch, as shown (1) by postmortem check, (2) by the return of the electrocardiogram to its first contour when the heart was restored to its original position, and (3) by the ability to repeat the same sequence of change twice in each of three animals. It appears proved from these experiments that the position of the heart does modify the electrocardiogram of bundle-branch block and can simultaneously completely reverse the direction of QRS in Leads I and III.

These experiments lend support to the contention presented in our previous communication,¹ viz.: "In the present state of knowledge and with the variability in direction of the QRS group which these experiments show can be produced by changing the position of the heart, it would be preferable not to attempt to locate the site of origin of ventricular extrasystoles and, for the same reason, bundle-branch block."

Furthermore, the argument that autopsy and electrocardiographic evidence do not correspond if the latter is interpreted according to the classical terminology, but do correspond if the Wilson terminology³ is applied, is not borne out when the data is critically examined. Mahaim⁴ has recently shown in an excellently carried out study and critique of reported observation that there is agreement in the majority of cases of his own series and those reported between the anatomical and electrocardiographic diagnosis when the latter is interpreted according to the classical terminology. He criticizes some of the earlier studies on the ground that the histological examinations were incomplete. Exceptions do occur, however, and, from our experiments, can be explained by alterations in the configuration of the heart due to position changes or preponderant hypertrophy of the ventricles. Such changes in the heart's configuration can be as great clinically as those produced in these experiments. This is evidenced by the marked alteration in the electrical axis in the plane of the leads encountered especially in left ventricu-

lar preponderant hypertrophy in which QRS is inverted in Leads II and III.

The contention presented here that the position of the heart modifies the electrocardiographic appearance of bundle-branch block is significant regardless of whether the classical or Wilson's interpretation of bundle-branch block is finally accepted as correct. Our results offer an explanation which will account for those apparent discrepancies between autopsy and electrocardiographic interpretations of bundle-branch block. It will

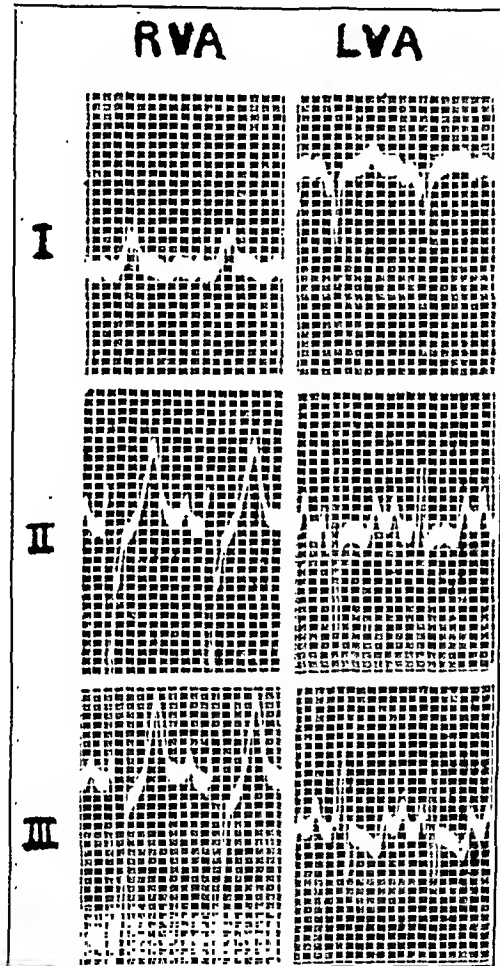


Fig. 3.—Segments of the three leads of the electrocardiograms taken in two positions of heart of Dog A13 to illustrate the complete reversal of QRS₁ and QRS₂ as in Fig. 2. RVA and LVA as in Fig. 2.

also avoid the difficulty of changing the interpretation from left ventricular preponderance to right bundle-branch block in cases such as we have seen and those reported by Luten⁵ and by Morris and McGuire,⁶ where the QRS complex, inverted in Leads II and III and of normal duration in a series of curves, shows a progressive increase in its duration beyond normal limits, or where a seeming right bundle-branch block would be called left ventricular preponderance when the abnormally long duration of QRS decreases to within normal limits. As stated previously by

one of us,⁷ it is more likely that when marked preponderance is present the bundle-branch block increases the duration of the QRS, and the preponderant hypertrophy determines the direction of the major initial deflection in the three leads.

We therefore advocate that no attempt be made in man to localize the bundle involved from the appearance of the electrocardiogram. Instead the diagnosis should be given as follows: 1, intraventricular block of the so-called bundle-branch block type, and 2, left (or right) axis deviation (or preponderant hypertrophy).

SUMMARY

It can be demonstrated that the contour of experimentally produced right bundle-branch block is modified by changing the heart's position. The direction of QRS can be reversed in Leads I or III, or in both, by moving the heart's apex from left to right of the body's long axis, especially when the heart is at the same time rotated on its own long axis. This shift alone may change a seeming right to a seeming left bundle-branch block or vice versa, depending on whether the classical or Wilson's terminology is used, as is shown in the illustrations of this report. This last observation explains the apparent discrepancies between the electrocardiographic and the autopsy diagnosis of the branch involved in bundle-branch block.

It is recommended that no attempt be made to designate the bundle-branch involved; instead in man all such cases should be called intraventricular block of the bundle-branch type.

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A STUDY OF VISCEROCARDIAC REFLEXES*†

I. THE EXPERIMENTAL PRODUCTION OF CARDIAC IRREGULARITIES BY VISCERAL STIMULATION

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THE clinical literature presents numerous cases in which an apparent correlation between visceral excitation or disease and cardiac irregularities existed. That such a correlation actually exists in man is definitely supported by the observations of Babcock,¹ Mayo,² and Straus and Hamburger³ who have reported cases of cardiac disorders that improved after biliary tract surgery.

Lennox, Graves and Levine⁴ in a study of forty-eight patients during surgical operation, as well as Marvin and his associates^{5, 6} in a similar study of sixty patients do not report any changes in the electrocardiogram which could be attributed to manipulation of the viscera.

Recently Ressinger,⁷ using needle electrodes, studied a few cases during abdominal and thoracic operations. In a case of cholecystectomy he observed that pulling on the liver caused a slowing of the heart rate and a disappearance of the P-wave. When the stimuli ceased, the heart became normal. In another case of carcinoma of the esophagus, a slight pull on the cardia caused an auricular flutter which went over into a fibrillation. The various waves of the electrocardiogram were markedly "splintered."

Experimentally it is established that cardiac inhibition or acceleration may be induced by visceral excitation. In the frog, tapping or stimulation of the viscera^{8, 9, 10} or incision of the gall bladder with a spillage of bile into the upper peritoneal cavity^{11, 12} causes reflex inhibition of the heart. In the turtle the same type of stimulation causes acceleration of the heart.⁹ In the dog, distention of the gall bladder may cause either an inhibition or an acceleration of the heart rate.^{12, 13} In nausea and vomiting, inhibition followed by acceleration is known to occur quite uniformly.¹⁴ Prolonged distention of the stomach causes acceleration of the heart in the dog; and in one out of twelve dogs studied by Burgess, Scott and Ivy,¹⁵ it caused the occurrence of rhythmically recurring ectopic beats. Percy and Howard¹⁶ observed occasionally premature contractions in dogs on distention of various viscera after poisoning the heart with barium chloride and found that the sympathetic pathway was concerned. This observation falls in line with the observations of

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Rothberger and Winterberg¹⁷ who were able to produce extrasystoles by sympathetic stimulation after small doses of barium chloride.

In view of the physiological and clinical importance of viscerocardiac reflexes and the rather meager experimental literature on the subject, Dr. A. C. Ivy pointed out that further experimental study of the subject was definitely indicated.

EXPERIMENTAL

ATTEMPTS TO PRODUCE EXTRASYSTOLES. PART I

The Occurrence of Spontaneous Extrasystoles in the Dog.—As a rule in the anesthetized animals the blood pressure record was observed for cardiac irregularities and then on observing irregularities, the animal was connected to the leads of the electrocardiograph. In experimental work of this nature it is necessary to establish a norm or control series or to ascertain the incidence of spontaneous cardiac irregularities under the experimental conditions to be employed.

For this purpose a "control group" of ninety-five barbitalized dogs was used to determine the incidence of extrasystoles in an experiment in which the operative procedure was quite constant. This group of dogs was used primarily for a study of diuresis by Owen and Ivy,¹⁸ and was subjected to such operative procedures as cannulation of the carotid, trachea and ureters. Nine of the dogs in this group showed an average of one extrasystole every ten minutes over a period of from one to three hours. Records of two to three hours in each of twenty-two dogs (23 per cent) showed only one or two extrasystoles. The remaining dogs (66 per cent) showed no cardiac irregularities other than the normal sinus arrhythmia. In the first group the cardiac irregularities were evident early in the experiment. Thus, in order to eliminate false interpretation of these spontaneously occurring irregularities, all animals used in this study were observed for one-half hour before subjecting them to any procedure for the production of extrasystoles or other cardiac irregularities.

Distention of the Abdominal Cavity.—Since distention of certain of the abdominal viscera leads to stretching of the abdominal wall, it was considered necessary to ascertain if intra-abdominal pressure changes per se would cause cardiac irregularities.

Distention of the entire abdominal cavity was produced in ten lightly barbitalized dogs by the use of an oxygen tank in circuit with a manometer and a small trocar. Intra-abdominal pressure was never allowed to exceed blood pressure more than 5 mm. Distention and deflation in these cases were not productive of cardiac irregularities, although heart rate was increased by distention.

Distention of the Esophagus in Dogs and Rabbits.—Distention of the esophagus was made possible by the insertion and anchoring of a bal-

loon approximately one inch above the hiatus of the diaphragm. In a series of five lightly etherized dogs, distention or sudden collapse of this area even after previous irritation with 5 per cent hydrochloric acid was ineffective in producing cardiac irregularities. On adapting the above procedure to barbitalized rabbits two out of five displayed extrasystoles on either the distention or the deflation. One of these gave an extrasystole on distention when both vagi were severed in the neck and the spinal cord sectioned between the fourth and fifth thoracic vertebrae. Attempts to sever the sympathetic supply to the heart in this animal were unsuccessful.

Sudden Distention of the Stomach.—Distention and sudden collapse of the stomach were obtained by the insertion of a balloon or an open-end cannula, which was tied in place by purse string sutures. In a series of ten barbitalized dogs, distention or sudden collapse after distention

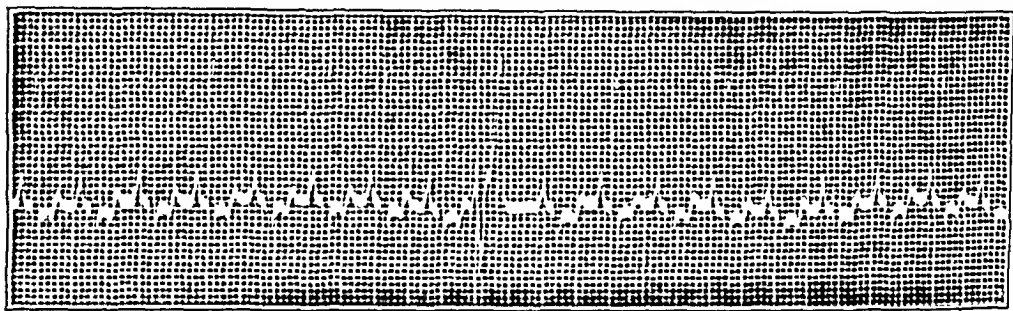


Fig. 1.—This is the electrocardiogram (Lead II) of one of the dogs (Dog M) that showed an extrasystole on belching produced artificially by distending the stomach. Note the extrasystole. The cardiac sphincter must be in tone in order to produce belching, otherwise when the air is injected into the stomach, it passes out of the esophagus.

of the stomach with one or one and one-fifth liters of air caused no cardiac irregularities although the heart rate was either increased or decreased. The response in cardiac rate even varied in the same animal from time to time, the rate generally being increased. In a series of ten lightly etherized dogs results similar to the above were obtained when an open-end cannula was used as an inlet and outlet for air to the stomach. Irritation of the stomach mucosa with 5 per cent hydrochloric acid followed by distention and deflation was not causative of cardiac irregularities in dogs. Adapting the above procedure to barbitalized rabbits, one out of four showed an extrasystole on distention of the stomach.

Belching.—Three out of eleven lightly etherized dogs, in which the stomach was suddenly markedly distended by blowing air into it and in which belching resulted, displayed extrasystoles with each eructation. This was obtained repeatedly in two of the dogs and in one it disappeared after section of the vagi. The vagi were not sectioned in the other two. In the third dog the distention of the stomach with belching caused extrasystoles (Fig. 1) at a frequency of three out of

fifteen trials. In this dog a definite pulsus alternans occurred frequently in periods of three to five minutes during and after distention on a number of trials. Belching could not be obtained unless the cardiac sphincter was in tone because the air passed directly out through the esophagus. When air was blown from the stomach out through the esophagus, extrasystoles did not result. Pilocarpine or epinephrine given to these dogs was without effect.

Because of the results on dogs, a series of twelve medical students who could swallow air and belch at will were studied. Electrocardiograms were made before, during the swallowing of air, and during belching. No cardiac irregularities nor significant changes in rate were observed.

Distention of the Duodenum.—Sudden increase or decrease of intra-duodenal pressure in a series of six barbitalized dogs did not cause cardiac irregularities although the heart rate was increased. The rapid injection of 50 c.c. of warm water (39° C.) into the duodenum of ten barbitalized dogs caused no change in the heart rhythm. However, in one of the ten the introduction of 50 c.c. of 0.4 per cent HCl at 39° C. caused a series of extrasystoles. In five lightly etherized dogs after irritation of the duodenum produced by injection of 5 c.c. of 5 per cent HCl, distention failed to cause extrasystoles.

Distention of the Colon.—Marked distention and sudden deflation of the entire colon in six barbitalized dogs caused no cardiac irregularities, although acceleration of the heart rate occurred.

In eight dogs the colon was surgically obstructed, the dogs surviving from one to three weeks. Although the colon became markedly distended and the animals toxic, no cardiac irregularities appeared in the electrocardiograms even as late as one hour preceding death.

Distention and Deflation of the Urinary Bladder.—Sudden distention and deflation of the urinary bladder in five barbitalized dogs did not cause cardiac irregularities. In five dogs under light ether anesthesia the same procedure failed to cause cardiac irregularities even after the irritation of the bladder with 5 per cent HCl.

Distention of the Biliary Passages in Anesthetized Dogs.—Distention of the biliary passages in ten barbitalized and in five lightly etherized dogs failed to produce cardiac arrhythmia. As found by others this procedure simply caused only a decrease or increase in heart rate.

Operative Procedures.—In only one out of eighty-five dogs used in this study did incision of the various viscera cause cardiac arrhythmia. In the one dog an extrasystole resulted on incision of the stomach. The manipulation of the abdominal viscera, such as occurs in abdominal operations, did not cause at any time cardiac irregularities other than a speeding or slowing of the heart rate. The spillage of the contents of the gall bladder, stomach, colon, and urinary bladder into the peritoneal cavity had no immediate notable effect on cardiac rhythm.

Distention of Viscera in the Presence of Spontaneous Extrasystoles.—As was pointed out above, spontaneous extrasystoles occur in 10 per cent of dogs under light ether or barbital anesthesia, when subjected to cannulation of the ureters. Only four dogs out of the eighty-five used in this study showed spontaneous extrasystoles prior to the introduction of procedures which, it was thought, might cause cardiac irregularities. Distention of the various viscera in three dogs did not apparently influence the sequence or frequency of the spontaneously occurring extrasystoles. In one dog, however, distention of the stomach increased the frequency of the extrasystoles sometimes.

ATTEMPTS TO PREDISPOSE OR SENSITIZE THE CARDIAC MECHANISM TO VISCERAL STIMULATION. PART II

It is evident from the preceding results that it is impossible in dogs to induce uniformly, or even frequently, cardiac irregularities other than acceleration or slowing of the heart rate by visceral stimulation. The fact stands, however, that extrasystoles and other irregularities do sometimes result. It is to be noted from the foregoing experiments that chemical irritation of the viscera did not definitely facilitate the elicitation of extrasystoles or other cardiac arrhythmias. It became obvious that if we were to secure cardiac irregularities other than changes in rate more uniformly, it was necessary in some way to sensitize or predispose either the cardiac centers in the central nervous system or the peripheral cardiac mechanism.

Barium Chloride.—Since Pearcey and Howard¹⁶ were able to obtain premature ventricular contractions by visceral stimulation after the administration of cardiotoxic doses of barium chloride, we decided to use this method. They state that when proper care was exercised in giving this agent intravenously, they could obtain cardiac disorders in "practically every animal used" on visceral distention.

We used five barbitalized dogs in which cardiac irregularities failed to appear on gastric distention. When we used the 2 to 8 mg. doses of Pearcey and Howard we failed to obtain premature contractions on distention of the stomach. However, one of the five dogs after receiving 40 mg. showed ectopic beats only on distention of the stomach, which appeared not to be due to the direct effect of the barium. We gave up this procedure because we could not feel absolutely certain that the irregularities one might obtain might not be ascribed to the direct effects of the barium itself on the heart.

Coronary Damage.—It was thought that damage to the left coronary artery might render the heart more susceptible to visceral influences. So, from seven months to one year prior to the visceral stimulation, the heart was aseptically exposed and the ramus descendens of the left coronary was damaged for 2 or 3 cm. along its course by dissecting it free and pinching it with forceps, the dogs being given parathormone

with the hope that an arteriosclerosis might result. (This work was done by Dr. Don C. Sutton who kindly gave me the dogs for my study.) Postmortem studies on the myocardium and the damaged vessels revealed definite pathological changes. Three dogs were available for visceral distention. Distention of the stomach, duodenum, biliary passages, and visceral manipulation failed to elicit cardiac irregularities; however, in one of these dogs distention of both the colon and the urinary bladder caused an extrasystole to occur.

In one of these dogs in which distention of the various abdominal viscera failed to cause an arrhythmia, extrasystoles resulted on dissection of the gastric vagi and on massage of the right stellate ganglion. A "control" series on this procedure was not made.

Experimental Hyperthyroidism.—Since cardiac disturbances are frequently associated with hyperthyroidism, it was decided to feed some dogs thyroid extract for a period prior to the distention of the viscera. Five dogs were fed 5 gm. of thyroid extract daily for a period of one week to ten days. This, of course, caused an increase in respiration and heart rate and a loss of weight and diarrhea. In one of the five dogs distention of the stomach caused extrasystoles, although no irregularities were noted prior to the distention. Distention of the duodenum and urinary bladder did not induce cardiac irregularities in these dogs.

Diphtheritic Myocarditis.—It was reported by Stewart¹⁹ that the injection of diphtheria toxin in appropriate doses would cause a myocarditis in dogs. It was hoped that myocarditis induced by this method would render the heart more susceptible to visceral influences. Five dogs were given 50 to 63 per cent of a minimum lethal dog dose of diphtheria toxin from five days to one week previous to the visceral stimulation. No cardiac irregularities were noted prior to the experiment. Light ether anesthesia was used in some of the dogs and light barbital in the others. In one dog distention and deflation of the stomach caused extrasystoles to appear. In another distention and deflation of the duodenum induced extrasystoles.

Epinephrine, Ephedrine, Pilocarpine and Nicotine.—In a number of dogs in which visceral stimulation failed to excite cardiac irregularities, an attempt was made to predispose the cardiac mechanism by injecting drugs which stimulate sympathetic or parasympathetic nerve endings. These attempts uniformly failed.

Jaundice.—Since biliary tract disease is rather frequently associated with cardiac disturbances^{1, 2, 3, 20, 21, 22, 23, 24} and since experimentally only inhibition or acceleration of heart rate usually occurs on distention of the biliary passages of normal anesthetized and unanesthetized dogs (Schrager and Ivy¹³ obtained extrasystoles in one of five dogs; Scott and Ivy¹² none in five dogs; and in my work, none in ten dogs), it is possible that biliary tract disease when present for a period of time may in some way predispose the heart to visceral influences. Further,

it is known that jaundice causes a bradycardia in young dogs,²¹ and increases vagal tone.^{21, 22} Buehbinder²⁵ observed a transient dislocation of the pacemaker in one dog ten days after the induction of jaundice, and spontaneous arrhythmias in frogs. Hence, it was thought desirable to produce obstructive jaundice in a series of dogs and to ascertain if this condition predisposes to cardiac irregularities on visceral stimulation.

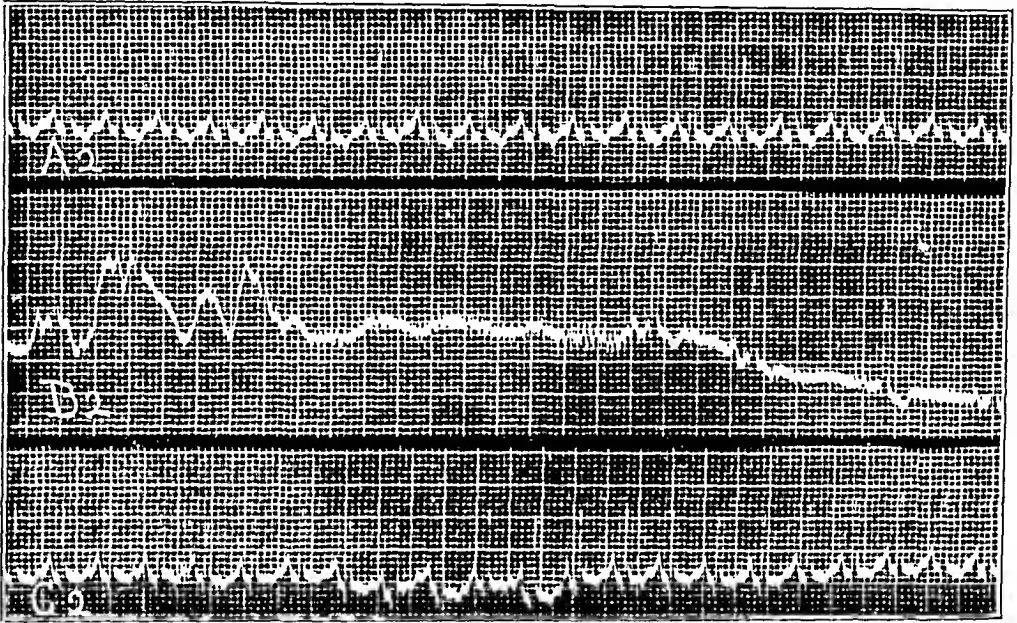


Fig. 2.—These electrocardiograms (Lead II) show a sinoauricular block which occurred (Dog T 11) during the bradycardia associated with vomiting caused by distention of the biliary passages in a dog jaundiced three weeks. A2, one week of jaundice and just preceding distention; B2, bradycardia and S-A block during distention and just after emesis; C2, release of distention.

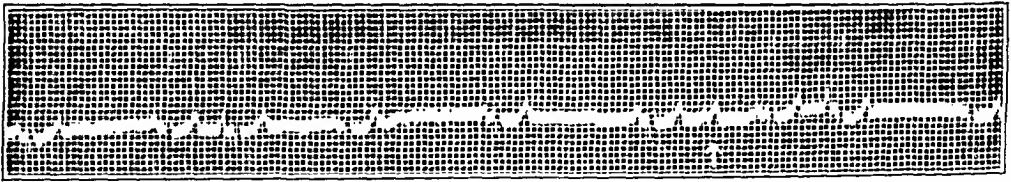


Fig. 3.—This electrocardiogram (Lead II) shows either a bizarre premature QRS complex or an extra-auricular beat, most likely the former, which occurred during a period of slight distention of the biliary passages in a dog (BT10) jaundiced eleven days.

Electrocardiograms were made on a series of five dogs and jaundice produced by aseptic ligation and section of the common bile duct. Electrocardiograms taken at intervals up to two weeks showed in one young dog one week after ligation, a shifting of the pacemaker within the sinus node, which did not exist before operation. Distention of the gall bladder and viscera under light ether anesthesia was performed in four of these dogs with well developed jaundice (one week). A ventricular extrasystole occurred in one on distention of the gall bladder.

In the belief that anesthesia might be a factor, it was decided to repeat these experiments on unanesthetized dogs. So a second series of five dogs with aseptic ligation and division of the common bile duct was prepared. Electrocardiograms (Leads I, II and III) before and after operation showed no cardiac irregularities. The gall bladder was then cannulated aseptically under anesthesia for purposes of distention of the biliary passages. The animals were permitted to recover and electrocardiograms (Lead II) were taken during distention of the biliary passages at various intervals up to three weeks. On distention of the gall bladder all dogs showed changes in cardiac rhythm. Slight distention sufficient to provoke nausea and vomiting always caused a marked

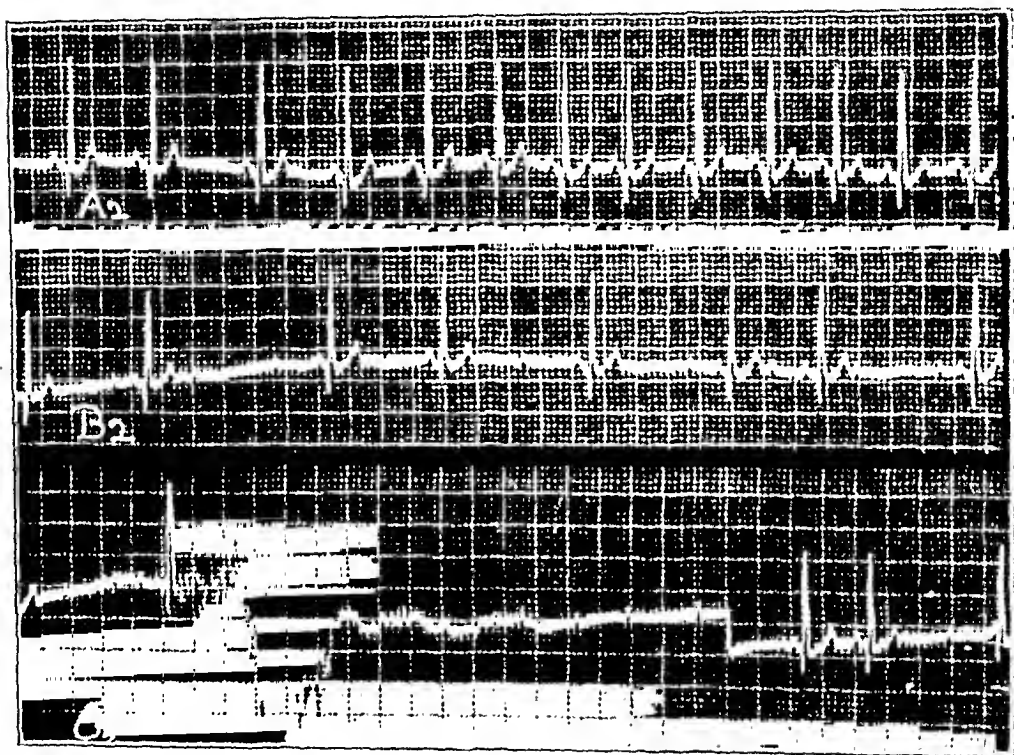


Fig. 4.—These electrocardiograms (Lead II) resulted from a dog (BT12) in which jaundice had been present for three weeks. A2, was taken before distention and is normal; B2, was taken during distention and shows a regularly occurring auricular ectopic beat or A-V block. C2 was taken during gagging produced by distention of the biliary passages and shows an A-V block. Other interpretations have been offered by experienced electrocardiographers.

bradycardia. In one dog a temporary complete sinoauricular block occurred (Fig. 2). In one either a bizarre premature ventricular complex or an ectopic auricular beat (Fig. 3), most likely the former, occurred occasionally during the bradycardia caused by slight distention. In one an ectopic auricular beat occurred during the bradycardia caused by distention and a heart-block (Fig. 4) shortly after retching. Recovery from bradycardia results very soon after release of the pressure and during continued distention the degree of the bradycardia may vary considerably.

SUMMARY AND DISCUSSION

Nine out of ninety-five anesthetized dogs in a group in which the carotid, trachea and ureters had been cannulated showed extrasystoles. Sixty-six per cent of the dogs in this group showed no extrasystoles at any time during the course of the experiment. Since extrasystoles occur "spontaneously" in dogs and in the course of any uniform operative procedure, it is necessary to observe the dog for some time after the necessary operative work has been done before one can determine whether or not a certain procedure will induce extrasystoles. In eighty-five dogs in which the carotid was cannulated and cannulae or balloons were introduced into the various viscera other than the ureters, only four manifested extrasystoles during a half hour observation period following the operative procedures. This does not indicate that the handling of the ureters is prone to lead to extrasystoles, since more visceral manipulation is required to cannulate the ureters than to cannulate or insert a balloon into the duodenum, stomach and gall bladder.

In experiments on eighty-two anesthetized dogs distention and deflation of the hollow organs failed to produce extrasystoles or other cardiac irregularities other than changes in rate. In one dog injection of 50 c.c. of 5 per cent HCl into the duodenum was followed by a series of extrasystoles. In other instances in which an attempt was made to irritate the hollow viscera by the previous injection of acid no cardiac arrhythmias occurred. In one out of eighty-five dogs an extrasystole resulted while holding the stomach with the fingers and incising it with the scissors. Distention of the esophagus produced extrasystoles in two out of five rabbits and of the stomach in one out of four. (The rabbit appears to be more "sensitive" than the dog.) Hence, in the normal unanesthetized dog, cardiac irregularities other than change in rate are very difficult to produce by distention or irritation of the abdominal viscera, but the significant fact is that in a few instances extrasystoles may be produced.

The most interesting observation made in the experiments on this group of animals is that belching caused extrasystoles in three out of eleven animals. Because the esophagus is so closely related to the right auricle it was thought that the extrasystole might be due to mechanical stimulation of the heart by the cructated bolus of air. This was not true in at least one of the dogs, since section of the vagi abolished the phenomenon. Also, in those dogs in which belching could not be produced because of an atonic cardiac sphincter, the rush of air through the esophagus failed to produce extrasystoles, and distention of the lower third of the esophagus was without effect. It appears that the cardiac sphincter must be in tone or the vagus must be hypertonic in order to obtain extrasystoles. However, pilocarpine or epinephrine given to the dogs in these experiments which did not manifest belching failed

to increase the sensitiveness of the mechanism. We believe that belching leads to cardiac irregularities through the same mechanism that is concerned in the production of cardiac irregularities which are associated with retching or vomiting, since belching and retching are closely related phenomena.

It is worthy of note that of the four dogs in which "spontaneous" extrasystoles were present marked distention of the stomach increased the frequency of the extrasystoles in one.

The results of the experiments designed to increase the irritability of the cardiac mechanism to visceral excitation indicate that such is the case. One of these dogs in which previous coronary damage had been produced showed an extrasystole on distention of both the colon and the urinary bladder. Extrasystoles were obtained on visceral excitation in two out of five dogs that had been given a sublethal dose of diphtheria toxin several days previously. Extrasystoles were obtained in one of five dogs previously rendered toxic by the administration of thyroid extract. Of the thirteen dogs used in this group of experiments, extrasystoles occurred in four on visceral excitation only.

The clinical and experimental literature cited above indicates that jaundice, biliary tract disease, or liver injury might lead to a sensitization of the mechanism concerned in the production of cardiac arrhythmias on visceral excitation. In one of ten dogs (one to three weeks), the production of jaundice caused a shifting of the pacemaker within the sinus node. In one of four anesthetized dogs in which jaundice had been present for one week, a ventricular extrasystole resulted on distention of the gall bladder. In five unanesthetized dogs marked and more uniform cardiac arrhythmias resulted on distention of the biliary passages, especially in three of the five. However, the arrhythmias were closely associated with or related in time of occurrence to the production of nausea and vomiting. Although the results indicate that anesthesia depresses and jaundice sensitizes the mechanism concerned in the production of cardiac arrhythmias on distention of the biliary passages, more experiments should be done and an analysis of the relation of nausea (denoted by salivation and smacking of the mouth) and vomiting to cardiac arrhythmias should be made. It was impossible for the author to undertake this phase of the problem, so it was turned over for further study to Dr. Crittenden, whose report will soon follow.

CONCLUSIONS

1. Distention, sudden collapse, or irritation of the hollow abdominal viscera rarely produces cardiac arrhythmias in anesthetized dogs. The fact remains, however, that extrasystoles do occasionally result, a fact which cannot be ascribed to coincidence and which is especially true of eructation of gas from the stomach. In twelve students no cardiac irregu-

larities occurred on belching. Marked distention of the stomach in the presence of preexisting extrasystoles may increase the frequency of their occurrence.

2. The results of experiments designed to increase the irritability of the cardiac mechanism concerned in the production of arrhythmias to visceral excitation indicate that such is the case. This is particularly true of common bile duct obstruction which results in jaundice and liver injury. In three of five jaundiced unanesthetized dogs, distention of the biliary tract caused either an ectopic auricular beat or heart-block, which was generally associated in regard to the time of occurrence with the appearance of retching or vomiting.

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A STUDY OF VISCEROCARDIAC REFLEXES*†

II. THE EXPERIMENTAL PRODUCTION OF CARDIAC IRREGULARITIES IN ICTERIC DOGS WITH AN ANALYSIS OF THE RÔLE PLAYED BY NAUSEA AND VOMITING

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THIS study was prompted by the work of Owen,¹ which indicated that marked cardiac arrhythmias may be obtained in icteric dogs following distention of the biliary passages. The occurrence of the cardiac arrhythmias was rather closely related to the appearance of nausea (denoted by salivation and smacking of the mouth) and retching. The experimental and clinical literature has been reviewed by Scott and Ivy² and Owen.¹

In this paper we shall report the results obtained from an electrocardiographic study on unanesthetized dogs and man on the following topics: (1) the effect of apomorphine subcutaneously; (2) the effect of atropine per se intravenously; (3) the antagonistic action of atropine on the action of apomorphine; (4) the effect of jaundice per se; (5) the effect of icterus on the action of apomorphine; (6) the effect of distention of the biliary passage in icteric animals; and (7) the effect of swallowing the stomach tube (ninety-two medical students).

EXPERIMENTAL

In order to determine the effect of vomiting per se on the heart, 0.1 grain of apomorphine was injected subcutaneously. To determine if the effects of apomorphine on the heart were due to vagal action from 0.2 mg. to 1 mg. per kilo body weight of atropine sulphate, dissolved in 0.9 per cent saline solution, was administered intravenously.

Dogs were used for all of the experiments except in those designed to determine the effect of gagging and vomiting caused by the passage of a stomach tube in man. All animals were unanesthetized. The dogs were rendered icteric by aseptically ligating and cutting the common bile duct. The ducts were obstructed ten days prior to the experimental procedure. Ten days were chosen as the best time for the introduction of the various procedures in the icteric dogs, since bile salts are at a maximum concentration in the blood about this time.³

Control electrocardiograms were made in all three leads before starting any procedure. All experimental reactions were recorded through Lead II. Care was taken in applying the electrodes to prevent drying

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and to avoid other variations in contact during the course of each experiment. Nausea is clearly indicated in the dog by salivation and smacking of the mouth and swallowing. The dogs were trained to lie quietly and did not move much during vomiting or the other procedures. The electrocardiograms were made under standard and as basal conditions as were possible in this type of work. Of course, the animals were active during retching and vomiting, but nevertheless lay relatively quietly on the table. None of the animals was moribund at the time the experiments were performed.

(1) *The Effect of Apomorphine Subcutaneously.*—Apomorphine was chosen because it causes marked nausea and retching, more marked

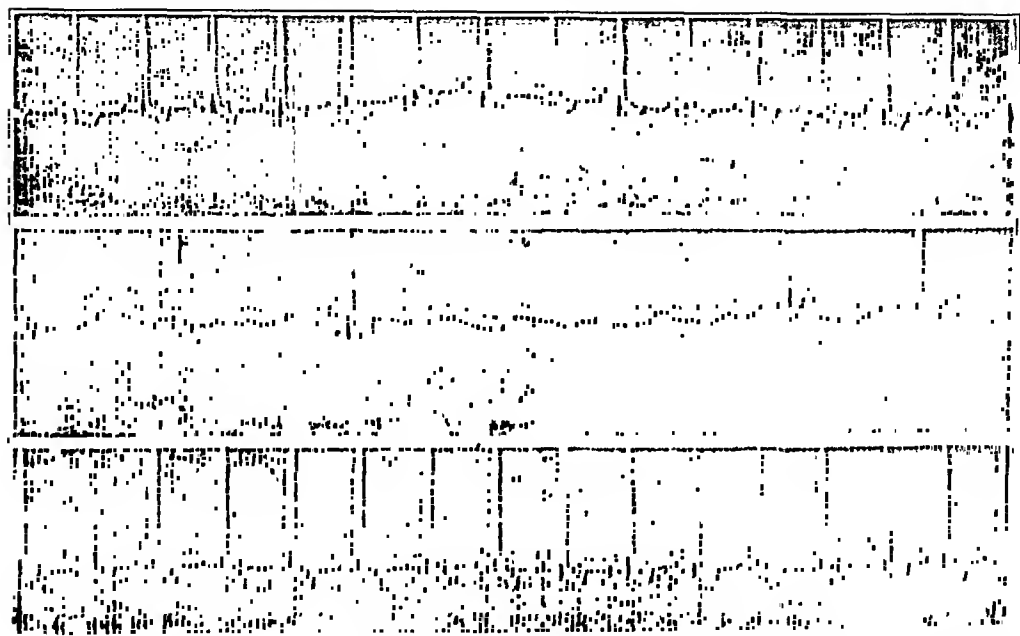


Fig. 1.—Dog No. 11. Normal animal. A₂, control lead two taken before the injection of apomorphine. B₂ is an electrocardiogram taken during retching. It shows a cardiac arrest and a bradycardia. C₂ shows the increase in rate due to nausea.

than that observed on distention of the biliary passages. It was believed that if electrocardiographic abnormalities were associated with nausea and retching, they would certainly occur after the administration of this drug. Thirty normal animals were used in this group. The onset of nausea, after the injection of the apomorphine, usually occurred within one or two minutes. Marked abnormal changes in the electrocardiograms were observed. During nausea an ectopic auricular beat in one animal occurred. Nausea did not occur in two of the animals. In arriving at the following interpretations due consideration was given to artefacts incident to skeletal movements. Certain bizarre changes which occurred when the animal was quiet may have been due to contractions of the stomach incident to vomiting. Such changes were called artifacts.

During retching, fourteen transient heart-blocks (A-V) were observed in eight of the animals; six heart-blocks were observed in one animal;

two in one; and one in six. In seventeen animals of the group, there were thirty cardiac arrests, or complete inhibition of the heart, varying from 1.2 seconds to 2.9 seconds. Nine transient periods of arrests occurred in one animal; five in one; and one each in fourteen. (A cardiac arrest was interpreted as being an inhibition of the heart in which the interval between beats was two or more times as long as the immediately preceding or following beats.) The animal which showed six heart-blocks and nine cardiac arrests also showed "auricular T-waves." A marked bradycardia was noted in one animal, in which the interval between beats was as long as 1.6 seconds to 2.1 seconds. An ectopic P-wave occurred once. In one animal, retching did not occur.

During vomiting, ectopic ventricular beats occurred in one animal and a pulsus bigeminus with ectopic ventricular beats in another.

Rate: Changes occurred in the P- and T-waves and in the QRS complex in a number of the animals, but nothing of a characteristic nature was noted. Nausea caused an average increase in the heart rate of 98 beats per minute (+6 to +186). Retching caused an average decrease of 126 (0 to -232). Immediately following vomiting the rate returned to the "nausea" rate. The rate changes were determined by comparison with the immediately preceding rate.

Summary.—These results show that rather marked electrocardiographic changes are associated with nausea, retching and vomiting. The changes are most marked during retching.

(2) *The Effect of Atropine per se Intravenously.*—Fourteen animals were used in this group. They received atropine sulphate intravenously. Two of them received 1 mg. per kg., the others from 0.2 mg. to 0.33 mg. per kg. The former dosage caused an increase in rate of 204 per minute. The other dosages caused an increase of from 36 to 174 with an average of 96 beats per minute. No marked changes in the electrocardiograms were noted following the atropine.

Changes in the P-wave: Seven animals did not show any change in the form of the wave. The remainder showed briefly the following changes: a maximum increase in the voltage of 1 mm. or a decrease in the voltage of 1 mm.; the wave became negative or was occasionally absent or diphasic; or the P- and T-waves fused.

Changes in the QRS complex: Five animals did not show any change in the form of the complex. The changes noted in the other animals were briefly as follows: an increase in R voltage of 6 mm. in two; a decrease of from 2 mm. to 6 mm. in four; a decrease in Q voltage in one; an increase in Q voltage in one; and the notching of R in one.

Changes in the T-wave: Six animals did not show any change in the T-wave. The following changes were noted in the other animals: the voltage increased 3 mm. in one; it became negative in two; occasionally negative in two; diphasic in one; occasionally diphasic in one; the wave disappeared in one; became occasionally absent in two; and absent in one.

(3) *The Antagonistic Action of Atropine on the Action of Apomorphine.*—Eleven of the animals in the above group were given apomorphine within two to five minutes after the injection of the atropine. The appearance of nausea was greatly delayed and often did not occur for from ten to fifteen minutes after injection. The phenomena of marked cardiac inhibition and heart-block did not occur in these animals. No nausea occurred in six animals; no retching in one; and no vomiting in one. A few changes in the P- and T-waves and in the QRS complex were noted, but they were not characteristic.

Rate: During nausea the heart rate showed an average increase of 53 beats per minute (+24 to +90); during retching it was decreased only 10 (−29 to +22); and during vomiting it increased 21 (−18 to +102).

Summary: These results clearly indicate that the pathway concerned in causing the electrocardiographic changes in the heart which are associated with nausea, retching and vomiting produced by apomorphine

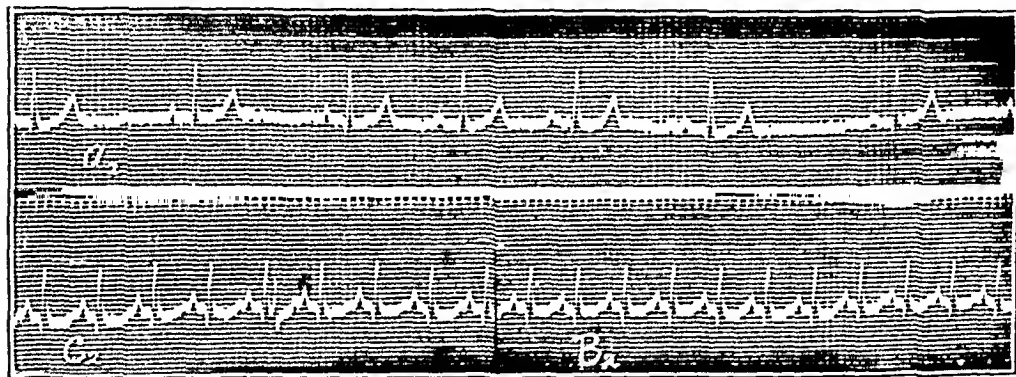


Fig. 2.—Dog No. 10. Normal animal. Lead II. *A*₂ is the control electrocardiogram taken before the injection of 1 mgr. per kg. of atropine sulphate. *B*₂ shows the effect of the atropine. *C*₂ was taken during nausea after atropine and apomorphine. An adventitious wave is seen which was interpreted as an artefact.

is via the vagus nerves. The tachycardia of nausea must be due to both increased activity of the sympathetic or accelerator mechanism and a decrease in vagal inhibitory tone, since apomorphine alone caused an average increase in heart rate of 98 beats per minute and after atropine an average increase of 53 beats.

(4) *The Effect of Icterus per se.*—Sixteen animals were used in this group. Control electrocardiograms were made before ligation and section of the common bile duct, and again ten days later before cannulation of the gall bladder for the purpose of distending the biliary passages. The degree of icterus in these animals varied as determined by the inspection of the sclera and subcutaneous tissues at the time of operation. All, however, were definitely icteric. According to these observations, two animals were slightly icteric; two were slightly to moderately icteric; seven were moderately icteric and five were markedly icteric.

Abnormal beats, which could be ascribed only to icterus, appeared in three animals. Ectopic ventricular beats were found in two; extra-

auricular in one. Some of the abnormal beats which were present before icterus, disappeared with icterus. These were the disappearance of "spontaneous" heart-block, or a rhythmically occurring auricular ectopic beat in two, and an extrasystole in one.

Rate: There was no change in rate in one. The rate was increased from 12 to 84 beats per minute in eleven and decreased from -6 to -72 in four. The rates were determined from the electrocardiograms only after a period of quiescence on the table.

Changes in the P-wave: No change occurred in Lead I in eight of the group. This wave became absent in four and negative in one.

No change occurred in Lead II in twelve animals. The wave became absent in one, negative in one, notched in one; a decrease in voltage was noted in three; and an increase in voltage up to 4 mm. was noted in one.

No change in the wave occurred in Lead III in ten animals. The wave became absent in one, negative in one, diphasic in one, and positive in one. The P-wave did not disappear from all three leads in the same dog.

Changes in the QRS complex: No change in Lead I was observed in four animals. Other changes were: a decrease in R voltage of 8 mm. in four, an increase up to 9 mm. in seven, and an increase in Q voltage in three.

No change in the form of the complex occurred in Lead II in two animals. Other changes noted were: an increase in R voltage up to 10 mm. in three; a decrease up to 11 mm. in one; an increase in Q voltage in three; a decrease in one; and the slurring of R in one.

No change was observed in the form of the complex in Lead III in four animals. Other changes noted were: the R became slurred in one, and notched in one; there was an increase in R voltage up to 13 mm. in four and a decrease up to 7 mm. in eight; and an increase in Q voltage in three.

Changes in the T-wave: No change in the form of the T-wave was observed in Lead I in five animals. The wave became absent in three, negative in one, and positive in one.

No change in the form of the wave was observed in Lead II in four of the animals. Other changes noted were: the wave became absent in two; positive in three; negative in four; diphasic in two; notching disappeared in one; there was an increase in voltage in one and a decrease in voltage in one.

No change in the form of the wave was observed in Lead III in four animals. The wave became absent in two, positive in two, negative in five, diphasic in two; and notching disappeared in one.

Summary: Icterus caused electrocardiographic irregularities to appear in three of the sixteen animals and to disappear in three. Various changes also occurred in the different waves in the three leads. The changes were so variable that we hesitate to interpret them.

(5) *The Effect of Icterus on the Action of Apomorphine.*—We desired

to ascertain whether icterus made dogs more sensitive to apomorphine in regard to the electrocardiographic irregularities associated with nausea and vomiting. Fourteen animals were used in this group. All of them were given apomorphine before obstruction of the common bile duct as a control. Eleven received apomorphine after production of icterus but before cannulation of the gall bladder and the others after either the first or second distention of the biliary system. The degree of icterus in these animals was determined as was noted above. Two animals were slightly icteric; two slightly to moderately icteric; four moderately icteric and six markedly icteric.

Nausea was not observed in four of these animals after apomorphine, and no abnormal beats were observed in the others during nausea. The

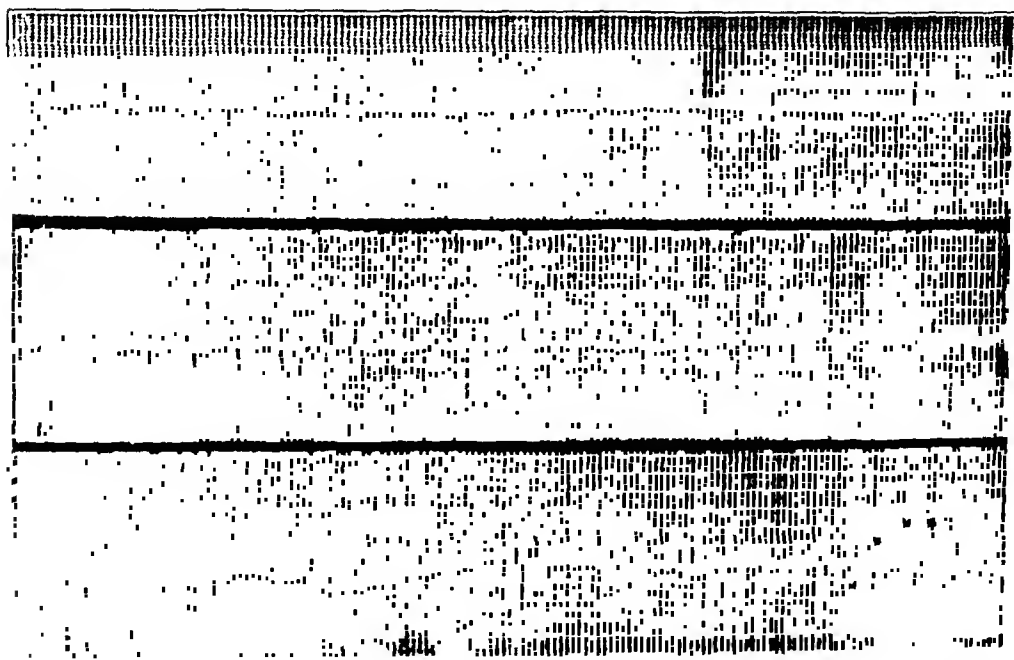


Fig. 3.—Dog No. 29. Moderately icteric. Lead II. A₁ is the control electrocardiogram taken before cannulation of the common bile duct. There is a sinus arrhythmia. A₂ is the control electrocardiogram taken ten days after ligation of the bile duct. It shows an increase in rate and possibly somatic tremors, although the dog was not visibly trembling. B₂ shows the effect of retching, following apomorphine in the icteric animal. It shows a return of the arrhythmia and an ectopic ventricular beat.

explanation of the absence of nausea in the four animals is not clear, especially since the onset of retching was not delayed. It is possible that icterus may depress the nausea mechanism in certain individual animals, since some animals appear to be depressed.

During retching five animals showed eight transient periods of A-V heart-block as compared to three periods of heart-block in three animals before they were icteric. There were fourteen cardiac arrests in ten animals as compared to eight arrests in seven animals before the production of icterus. Four of the five animals had not shown heart-blocks previously, and five of the ten had not shown cardiac arrests before icterus. One animal showed a high grade block with "auricular T-waves,"

and another animal manifested interpolated beats. In another animal there were ectopic ventricular beats in which the R-wave was absent, the S voltage was 22 mm. and the following T voltage 8 mm. (Fig. 3).

During vomiting one animal showed interpolated beats and two a marked bradycardia after vomiting instead of the previously existing tachycardia of nausea.

Rate: Nausea caused an average increase in the rate of 72 beats per minute (+25 to +126). Retching caused an average decrease of 102 (-46 to -140); and vomiting an average increase of 115 beats per minute (+59 to +153). These changes were in general less than those observed in nonicteric animals. Changes in the form of the various waves occurred in a number of animals, but nothing of a characteristic nature was observed.

Summary: The changes noted in this group of animals did not parallel the degree of icterus of the sclera and subcutaneous tissue. However,

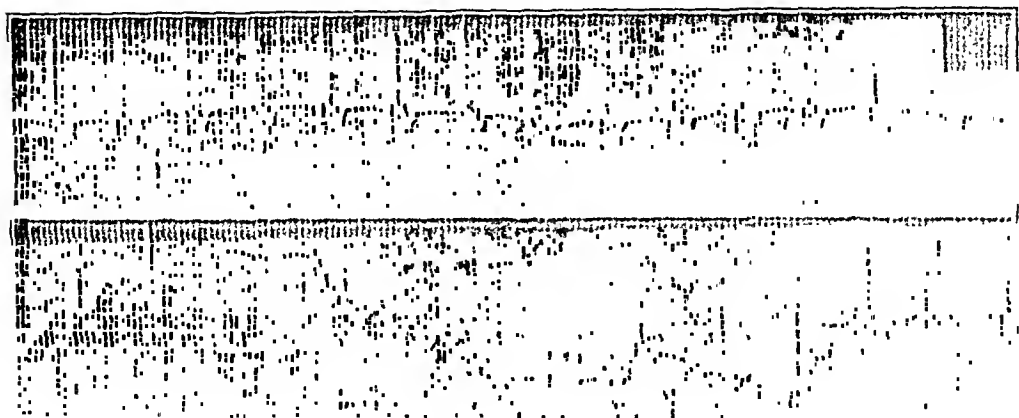


Fig. 4.—Dog No. 14. Markedly icteric. Lead II. A₂ is the control electrocardiogram taken before the distention of the biliary system. The inverted T-wave is normal for this dog. B₂ shows a cardiac arrest (3.36 seconds) due to severe pain (no retching was observed) caused by distention of the biliary system.

the changes indicate that icterus does "sensitize" the heart to the electrocardiographic abnormalities associated with retching. This statement is based primarily on the comparison of the marked abnormal cardiac changes noted above.

(6) *The Effect of Distention of the Biliary Passage in Icteric Animals.*—A control series on the effect of distention of the biliary passages in nonicteric dogs was not studied by us since in this laboratory a series of twenty dogs has been studied electrocardiographically. Extrasystoles occurred in only one of this group, only a tachycardia or a bradycardia being otherwise observed.

Fifteen animals were used in this group. They were rendered icteric by ligating and sectioning the common bile duct. The biliary system was distended ten days later by injecting from 40 to 100 c.c. of warm water through a syringe into the cannulated gall bladder. Because icterus increased the friability of the biliary system, satisfactory results

on distention, i. e., without leakage around the cannula, were obtained in only six animals. Three of these were moderately icteric, and three markedly icteric. In three of the animals the biliary system was distended a second time, on the day following the first distention. The cannula began to leak at this time. Hence the results in this group refer to nine distentions in six animals. This adds six animals to the series of Owen.¹ No nausea occurred in two distentions, no retching in six, no vomiting in three, and no apparent pain in three.

A cardiac arrest occurred in one animal after vomiting, and in another during pain (Fig. 4). Ectopic ventricular beats were noted in three animals during pain and in another during nausea. An extrasystole occurred in one animal during nausea and in another during pain. In one of the markedly icteric animals, the heart stopped for 2.16 seconds during marked pain. Late during the period of continued distention, after the pain, nausea, retching and vomiting responses were no longer acutely manifest, cardiac irregularities were rare. The various waves were studied carefully, but nothing of a characteristic nature was noted.

Rate: Mild distention either increased or decreased the rate; the average decrease was 30 beats per minute and the increase 27. The effect of nausea on the rate also was variable. Retching decreased the rate from 15 to 36 beats per minute. During and just after the act of vomiting, the rate was either decreased or increased. Pain was associated with a decrease or increase in rate (-36 to +42). Following distention the rate varied. It usually returned to normal within about five minutes.

Summary: Changes in this group more closely parallel the degree of icterus than did those noted above in the icteric animals receiving apomorphine, probably because distention of the biliary passages is a sub-maximal stimulus. Owen¹ studied the electrocardiographic changes on distention of the biliary system in icteric animals, and observed the same marked changes which we observed in this group of animals. He thought that the presence of preexisting icterus in dogs sensitizes the mechanism concerned in the elicitation of cardiac irregularities. Our results, we feel, add further evidence that icterus may sensitize the cardiac vagal mechanism. Since the cardiac irregularities were associated primarily with pain, vomiting or retching, and were not observed during continued distention when there were no objective manifestations of acute pain and retching, and since atropine abolishes most of the irregularities, these irregularities must be due to a motor discharge sent out over the vagi as the consequence of acute pain sensations and particularly of the sensory impulses which provoke retching.

(7) *The Effect of Nausea and Retching Produced by Swallowing the Stomach Tube in Man.*—Of the ninety-two students who swallowed the stomach tube in these experiments, eleven did so with no difficulty (no gagging), fifty-nine with difficulty (gagging), and twenty-two with marked difficulty (gagging and vomiting). In these students the con-

trol electrocardiograms showed ventricular extrasystoles in two, and ectopic ventricular beats in another.

During the passage of the stomach tube, A-V blocks occurred in three.

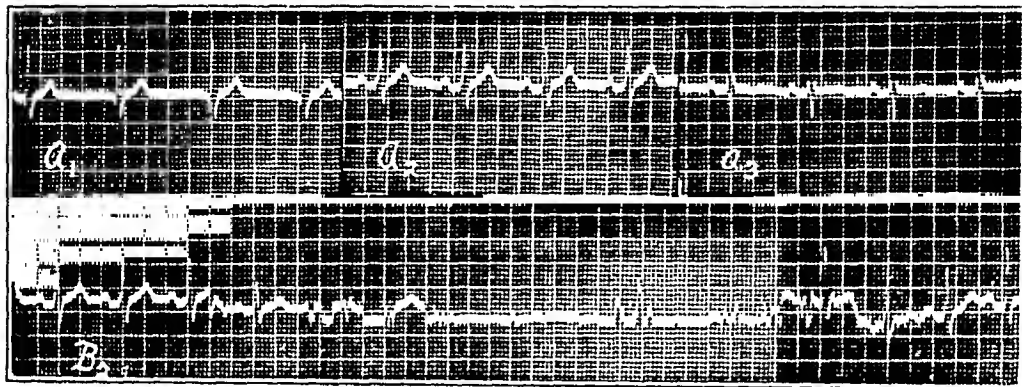


Fig. 5.—Student B. A_1 and A_2 and A_3 are the control electrocardiograms in all three leads taken before swallowing the stomach tube. B_2 shows a prolonged ventricular standstill, and a possible A-V block, which occurred during gagging while swallowing the tube. The student felt faint and dizzy.

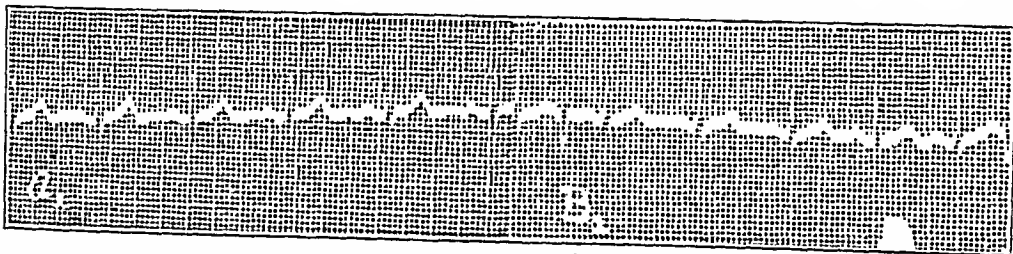


Fig. 6.—Student S. Lead II. A_2 is the control electrocardiogram. B_2 was taken while the student was swallowing the stomach tube and shows ectopic beats which occurred during gagging and just after the T-wave each time.

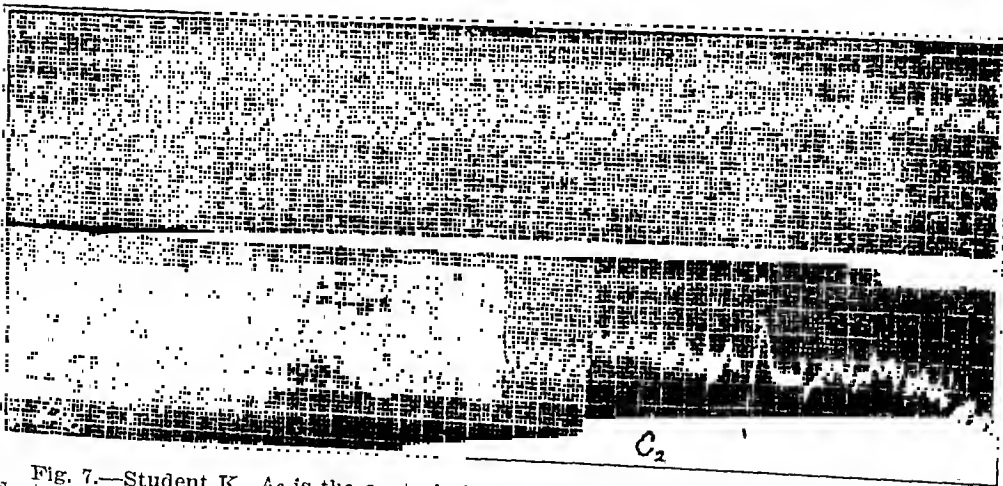


Fig. 7.—Student K. A_2 is the control electrocardiogram. B_2 was taken while the student was swallowing the stomach tube and shows primarily an increase in rate, which occurred early soon after the tube was started. (The film was inverted by the photographer.) C_2 shows a ventricular extrasystole which occurred during gagging.

In one of the students the ventricular arrest was so prolonged that six seconds elapsed between normal ventricular beats. Ventricular extrasystoles were noted in one and an extrasystole of auricular origin in two. Ectopic ventricular beats were noted in five.

The various waves were studied carefully but nothing of a characteristic nature was detected.

Rate: No change in rate was observed in one student who had no difficulty in swallowing the tube. The rate was increased 28 (average) beats per minute (+6 to +72) with no gagging, increased 41 (-6 to +79) with gagging, and 45 (+16 to +78) with vomiting. It is interesting that only one student manifested inhibition during gagging, which stands in marked contrast to the dogs.

DISCUSSION

The results, following the injection of apomorphine in normal animals, show that nausea, retching and vomiting (especially retching) cause marked cardiac irregularities. Not only do changes in rate occur, but also changes in the form of the various waves, heart-block, and arrest result.

Since it is known that stimulation of the peripheral end of the vagus not only affects the rate of the heart, but also impairs conductivity and may produce A-V blocks, it was reasonable to assume that the changes incident to nausea and vomiting might be abolished by atropine. This proved to be true. These changes indicate that when the vomiting center, or nausea mechanism, is strongly excited, along with the motor discharge that passes out to the stomach from the vagus center, a discharge arises from the cardio-inhibitory center which passes to the heart via the vagi and markedly modifies cardiac activity. A maximum excitation of the vomiting center must be present before the cardio-inhibitory center is sufficiently affected to produce heart-block, since the nausea and vomiting induced in nonicteric dogs by distention of the biliary passages does not cause marked changes. Apomorphine in the doses used certainly produces maximum excitation of the center.

Since bile salts increase the tone of the vagus, it was thought that ieterus would increase the cardiac irregularities after apomorphine and after distention of the biliary passages. Our results indicate that this is the case.

Ieterus per se gave variable results. We had expected more irregularities due to ieterus without the introduction of an additional factor. It was noted that cardiac ectopic beats occurred after ieterus, but in some of the animals such beats disappeared after the animals were icteric. The accentuation of the sinus arrhythmia as reported by Buchbinder⁴ and anticipated by us was not observed. The rate changes were not consistent, as was found by Buchbinder,⁴ but the tendency was toward an increase in the majority of animals. Although we were not certain of the ages of the animals, the four in which the rate was decreased were relatively young dogs. The depth of the icteric coloration of the sclera did not parallel the extent of the cardiac irregularities.

The results, in the icteric animals receiving apomorphine, showed more

cardiac irregularities than were noted before the animals became icteric. If icterus sensitizes the vagal mechanism as we believe, then our results are in accordance with such a hypothesis. Although the irregularities did not parallel the degree of icterus, it must be kept in mind that apomorphine is a maximal stimulus in producing nausea, retching and vomiting. With a submaximal stimulus, as we shall see below, the results do parallel the degree of icterus.

The distention of the biliary system caused nausea, retching, vomiting and pain. These symptoms were associated with cardiac irregularities which closely paralleled the degree of icterus as was expected. Schrager and Ivy,³ Scott and Ivy,² and Owen¹ in the distention of the biliary system of twenty unanesthetized and nonicteric animals observed cardiac ectopic beats in only one animal which may have had a "sensitive" heart to begin with. Our results when compared with theirs support the hypothesis that icterus sensitizes the cardiac vagal mechanism. Owen, however, in the distention of a group of anesthetized icteric animals failed to obtain cardiac irregularities which he and we observed in unanesthetized dogs. This difference is obviously due to the fact that anesthesia depresses the vomiting reflex.

The results on the students are especially interesting when compared to the results obtained in the first group of animals receiving apomorphine. It was noted that the rate changes in the dogs were much more marked than those in the students. Only one student showed a decrease in rate and this was very slight, while in the dogs nausea and vomiting were accompanied by a tachycardia and retching by a bradycardia. Two factors may play a rôle in these differences. The stimulus used for the dogs was maximal (apomorphine) while that for the students was submaximal. Also the origin of the reflex in the dogs (distention of bile passage) was abdominal while in the students it was pharyngeal. The origin of the reflexes may play a rôle even though the end-result, nausea and vomiting, are the same. However, the results on the students are more analogous to the results obtained in nonicteric dogs on distention of the biliary passages.

The abnormal beats observed in the students indicate that "sensitive" hearts may react to swallowing the stomach tube. It would seem that if the retching were marked, in some instances it might be serious. For instance, the student in whom there was a prolonged ventricular standstill, reported that he felt very ill and dizzy while swallowing the tube. It seems possible that such an arrest may be sufficiently prolonged in certain cases to prove fatal. Recently there have been reported to us two cases of sudden death on passage of a stomach tube. One was a postoperative case of carcinoma of the stomach, which was to be treated by lavage. The passage of the stomach tube resulted in sudden unexplained death. The other case had carcinoma of the cardia with an angina pectoris. In this patient an attempt was made to secure gastric contents

for a gastric analysis. During passage of the stomach tube, the patient stated that he felt very ill, and as the tube was being withdrawn, he died.

SUMMARY

The results of this study seem to indicate clearly that nausea, retching and vomiting (induced by the subcutaneous injection of apomorphine) may cause in normal unanesthetized dogs cardiac irregularities, such as heart-blocks, cardiac arrests, ventricular and auricular ectopic beats. These are most likely to occur during retching. There were also changes in rate, nausea causing usually a tachycardia and retching a bradycardia.

The intravenous injection of atropine almost completely inhibited the cardiac irregularities associated with nausea, retching and vomiting following the injection of apomorphine. The results indicate that during marked excitation of the vomiting center the cardio-inhibitory mechanism is affected, the degree to which it is affected depending upon its sensitivity.

Icterus per se caused both the appearance and the disappearance of electrocardiographic abnormalities in a few instances. The changes in rate were variable, but the tendency was towards an increase. Slowing of the heart rate, however, may occur. Preexisting icterus increased the occurrence of the cardiac irregularities which are associated with the elicitation of nausea, retching, vomiting and pain by distention of the biliary passages. The irregularities following the injections of apomorphine could not be said to parallel closely the degree of icterus; but the changes due to distention of the biliary system did parallel the degree of icterus. This may have been due to the probable fact that apomorphine is a stronger stimulus. The results of the experiments on the icteric animals, we believe, indicate that icterus sensitizes the cardio-vagal mechanism.

Electrocardiographic abnormalities, such as extrasystoles, arrests, ectopic, ventricular, A-V blocks, etc., occurred in 10 per cent of the students while nauseated or retching during the swallowing of a stomach tube. No change in the rate was observed in one student. In the others there was an increase in rate which was dependent upon the ease with which the tube was swallowed. It is interesting to note that a bradycardia did not occur, whereas in dogs during retching bradycardia occurred very uniformly.

In all experimental procedures, changes in the P-wave, the QRS complex and the T-wave occurred, none of the changes being characteristic.

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THE SIGNIFICANCE OF LARGE Q IN LEAD III OF THE ELECTROCARDIOGRAM DURING PREGNANCY

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PARDEE¹ has called attention to the occurrence of a large Q-wave in Lead III of the electrocardiogram. Briefly he defined it as a Q-wave in Lead III 25 per cent or more of the largest excursion of the QRS in any lead. He found this condition present in 7 per cent, or fourteen of 200 cases of heart disease of various sorts. Eight of his fourteen examples of deep Q₃ occurred in thirty patients who had the anginal syndrome. The remaining six records showing deep Q₃ were distributed among 170 patients suffering with heart disease other than angina. In a series of 277 records from normal hearts which he also reported only two showed the condition. Pardee also observed that a large Q₃ could occur during pregnancy and disappear after delivery and that it was profoundly affected by respiration. Nevertheless, he concluded that a deep Q₃ represents an impairment of the left ventricle, in most instances due to coronary narrowing. Willius² concurred in these views. He found 300 records which showed deep Q₃. Of these 300 records, 89.3 per cent "were obtained in examination of patients who had one of the following conditions: hypertensive heart disease, the anginal syndrome, hypertensive heart disease accompanied by the anginal syndrome, or arteriosclerotic heart disease not accompanied by the anginal syndrome or hypertension." There were only three cases, or 1 per cent, in which the patients had normal hearts. In a group of 977 normal patients, only two cases, or 0.2 per cent, showed large Q₃. Therefore, Willius believes deep Q₃ to be an additional diagnostic sign of heart disease. Fenichel and Kugell³ made observations which corroborated this work. They also correlated the electrocardiographic and post-mortem findings in thirty-five cases. Twenty-seven cases showed at post-mortem examination myocardial fibrosis or infarction; seventeen of these twenty-seven had shown large Q₃ in electrocardiograms, only ten did not show large Q₃. In the remaining eight cases electrocardiograms had shown no large Q₃ waves, and there was no evidence of myocardial damage at post-mortem.

While studying axis deviation of the electrocardiogram during the

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course of pregnancy, we selected those records which showed a large Q_3 strictly according to the criteria of Pardee.¹ The criteria are: (a) that Q_3 should be 25 per cent or more of the greatest deflection from the base line of the QRS complex in any lead; (b) that no records should have R_3 greater than R_2 , none should show right axis deviation; (c) that an R_3 must be present; (d) that S_3 must be absent; (e) that no "vibratory" or irregular QRS complexes of the "M" or "W" types in Lead III should be present. We have separated those records which show a deep Q_3 wave only transiently, appearing and disappearing apparently with phases of respiration. A deep Q_3 selected according to these criteria was continuously present in the records from 17 of 342 cases. It occurred transiently in the records of 9 additional cases. Counting only the 17 in which the sign was continuously present, the incidence of deep Q_3 in our series is slightly less than 5 per cent as compared with 7 per cent in Pardee's 200 cardiac patients¹ and 0.42 per cent of approximately 70,000 records searched by Willius.²

Our series is made up of electrocardiograms taken from pregnant women referred privately or to the cardiac clinic of the Boston Lying-in Hospital for estimation of their cardiovascular status. The diagnoses in the 342 patients whose electrocardiograms were studied were as follows: rheumatic heart disease was diagnosed sixty-six times, congenital heart disease five times. There were two patients with hypertension and one with active rheumatic infection and one with questionably active rheumatic infection. In twenty-three cases there were extremely loud systolic murmurs, loudest at the base especially in the pulmonic area, which seemed too intense to be functional and yet on careful consideration could not definitely be diagnosed as either congenital or acquired heart disease. We suspect that these murmurs are associated with the changing position of the heart during pregnancy. The remaining 244 cases showed no cardiac pathology. To be sure, all of these 244 patients were referred to the heart clinic of the hospital for an opinion because they had signs or symptoms which suggested the possibility of heart disease to the house officers in the routine admission physical examination. The signs and symptoms which attracted their attention were systolic murmurs, moderate or faint at the base, and best heard in the pulmonic area; reduplicated first or second sounds; simple sinus tachycardia; or extrasystoles. A few had a story of mild palpitation which may have been paroxysmal tachycardia. Complaints of vague palpitation, breathlessness, night starts and a sense of weakness also served to send some of the patients in this group to the heart clinic. In none of these 244 patients was organic heart disease found. The signs and symptoms merely arrested the attention of the routine examiner who referred the patient for special examination. The group cannot, in any way, be considered a group of patients with abnormal hearts. They were examined carefully to determine whether they had heart disease and were

found to have none. They are, therefore, more clearly a normal group so far as their hearts are concerned than would be any unselected group of pregnant women.

In Table I are tabulated the 17 cases, the records from which showed deep Q_3 continuously present. Among these, there was one patient with definite rheumatic mitral stenosis, one with questionable rheumatic mitral regurgitation, and one with active rheumatic infection, that is, two or at the most three cases of organic disease in the 17 showing a deep Q_3 -wave in all complexes of Lead III. One patient died of eclampsia post partum, but there was no evidence of eclampsia when the electrocardiogram was taken. In the remaining 13 patients there was no organic cardiac pathology. There was no evidence of the anginal syndrome in any patient in this series.

Should a deep Q_3 be related to organic change in this series, we would expect to find evidence of such change present in a greater number of those patients whose electrocardiograms exhibited the deep Q-wave in all complexes of Lead III. Only 17.6 per cent of the seventeen patients continuously showing deep Q_3 had organic heart disease, while in the series as a whole 21.6 per cent were diagnosed as having definite organic cardiac change. To present the results even more clearly:

Among 98 patients with organic or doubtful heart disease deep Q_3 was found 3 times (3 per cent).

Among 244 patients with no heart disease deep Q_3 was found 14 times (5.7 per cent).

All but six of the seventeen electrocardiograms which continuously showed deep Q_3 were taken in the sixth month of pregnancy or later. Like Pardee¹ we found that R_1 was greater than R_2 in the majority of the cases showing deep Q_3 . In one of them R_1 equaled R_2 , the Q- and R-waves in Lead III nearly balancing each other. The presence or absence of the various waves and the positive or negative quality are indicated in Table I. The finding of greatest significance is that T_3 is inverted in sixteen cases and is flat in the remaining one. Of almost equal importance and of similar significance, as will be discussed below, is the fact that in twelve of the seventeen cases P_3 is variable, that is, positive, negative or iso-electric. The P-wave is flat in one and upright in only four. The actual axis deviation according to the criteria which we use (White⁴) was normal except for one instance of left axis deviation.

In Table I are also tabulated the nine cases showing marked variation of Q_3 , presumably respiratory. At its least value Q_3 is less than 25 per cent of the greatest QRS in any lead of the same electrocardiogram, or absent entirely, while at its greatest it is at least 25 per cent of the maximum QRS in any lead of the same electrocardiogram. These nine cases are not grouped with the seventeen just discussed because the deep Q_3 was not continuously present. They show that deep Q_3 in some cases is in-

constant and freely variable. We wish to call attention particularly to the following findings: in seven of these nine cases T_3 is inverted and in the other two is flat. P_3 is inverted in one case, varies from inverted to slightly positive in six and is upright in two. The axis is normal in six, shows left deviation in one, and varies from normal to left in two. In all except two the electrocardiograms were taken in the sixth month or later.

DISCUSSION

In our opinion, these findings in pregnant women indicate that a large Q_3 may result from a change in position of the heart. This may arise from a more transverse position of the heart or from rotation of the heart on its own long axis or a combination of these two. Several contributions to the literature concerning the influence on the electrocardiogram of the position of the heart in space are of interest in this connection. Cohn⁵ by rotating the leads of the electrocardiogram taken directly from the chest in a clockwise manner 80 and 120 degrees produced curves showing typical large Q_3 -waves. He points out that these electrocardiograms are essentially those of left axis deviation as would be expected from the angle of the heart in respect to the rotation of the Einthoven triangle. It is important, however, that these artificial curves differ from true left axis deviation in one respect, the P_3 - and T_3 -waves are inverted, i. e., are in the same direction as the QRS complex in Lead III. This corresponds to the result of Bland and White's study⁶ of complete inversion of Lead III due to transverse position of the heart. Findings of similar significance in regard to the inverted T-wave in Lead III associated with left axis deviation comes from studies on the electrocardiogram in obesity.^{7, 8} This evidence from the literature points to the possibility that inverted T_3 and P_3 are characteristic of transverse position of the heart. In our experience inverted T_3 and low, iso-electric, inverted or variable P_3 are commonly associated with the presence of large Q_3 (see Table I).

Our findings in pregnant women, both with and without heart disease, in whom we relate the occurrence of deep Q_3 to the transverse position of the heart, suggest that in nonpregnant patients a deep Q_3 may be associated with a particular body type, characterized by a relatively short, thick trunk and high diaphragm (a type traditionally subject to degenerative vascular disease), rather than with organic change in the heart muscle itself. Certainly a sign which can so readily be produced by change in position of the heart would seem to be unreliable as an aid in the diagnosis of organic disease of the myocardium.

*This table gives the details of the electrocardiograms discussed in the text. The third column gives the month of pregnancy in which the electrocardiogram was taken.

+ = upright P, R and T or a downward Q and S.

Blank = absent or iso-electric waves as indicated.

- = inverted waves.

± = diphasic waves.

θ = low, indefinitely shown or variable (slightly up, iso-electric, or slightly inverted) waves.

SUMMARY

A large Q_3 as defined by Pardee was found in seventeen of the 342 pregnant women. This is slightly less than 5 per cent. Ninety-eight of these women had organic heart disease or signs which justified a diagnosis of possible organic heart disease. Only three of these cases had large Q_3 —slightly more than 3 per cent. Two hundred and forty-four of the women had no organic heart disease. Fourteen of these had large Q_3 (5.7 per cent).

The anginal syndrome was not present in any of this series, nor have we ever found it in a pregnant woman.

A large Q_3 may occur transiently, apparently modified by phases of respiration. We found nine such cases in this series.

A large Q_3 is frequently associated in this series with inverted T_3 and low or inverted P_3 . These findings are characteristic of transverse position of the heart according to evidence from the literature.

The comparatively frequent occurrence of large Q_3 during pregnancy in patients with normal hearts, as contrasted with its reported rare occurrence in series of patients with normal hearts where pregnancy was not mentioned and probably was rarely present, suggests that a large Q_3 may be related to a transverse position of the heart such as occurs during pregnancy. In our opinion, therefore, a large Q_3 is not reliable as a sign of heart disease.

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ELECTROCARDIOGRAPHIC AND BLOOD PRESSURE CHANGES IN EXPERIMENTAL PERICARDIAL EFFUSION AND OCCLUSION OF THE VENAE CAVAE*

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CHANGES in the ST-segment of the electrocardiogram have been studied since 1909, when Eppinger and Rothberger¹ observed such changes in dogs following the injection of silver nitrate into the heart muscle. Their work was confirmed by others. In 1918 Smith² produced ST changes in dogs by ligation of the coronary arteries, and in 1919 Herrick³ described such changes in clinical cases of coronary occlusion. A large mass of literature has accumulated with regard to these changes, and it is generally agreed that marked changes in the ST-segment are particularly frequent when there are infarctions near the apex. Changes in the ST-segment have been observed also in pneumonia,⁴ in rheumatic fever,⁵ after the use of digitalis, and, combined with changes in QRS, in bundle-branch block.

In 1929 Porte and Pardee⁶ reported ST changes in patients with pericarditis. They did not consider specifically the question of pericardial effusion, but at least one of their patients had an excess of fluid in the pericardium as shown by the postmortem examination. Scott, Feil and Katz⁷ reported the occurrence of marked ST changes in patients with pericardial effusion, notably one with an aneurysm which had ruptured into the pericardium and without active inflammatory changes or coronary disease. The same group of workers⁸ reported at the same time a series of experiments on dogs in which they found elevation and convexity of the ST-segment, inversion of the T-wave, and shortening of the ST interval following the injection of fluid into the pericardium at various pressures. Foulger and Foulger⁹ have confirmed these findings. We have failed to find in the literature any previous description of ST changes in pericardial effusions, although in several reports a casual mention of reduced QRS amplitude was encountered. Padilla and Cossio¹⁰ have since reported changes in two patients, and Harvey and Scott¹¹ in one, similar to those reported by Scott, Feil and Katz.

The occurrence of ST changes similar to those of coronary disease in other conditions appears to justify experimental study with a view to learning the mechanism of the change.

EXPERIMENTAL OBSERVATIONS IN PERICARDIAL EFFUSION

The first portion of this report is concerned with a series of thirty experiments on nineteen dogs involving pericardial effusion obtained artificially

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by a method similar to that used by Katz, Feil and Scott. The pericardial pressure was recorded on a smoked drum by means of a mercury manometer. Tracings were made simultaneously of the pressure in the carotid artery with another mercury manometer. Electrocardiographic tracings were made by the three leads customary in the human electrocardiogram. In a few experiments the chest was allowed to remain open, and artificial respiration was maintained throughout the experiment; this did not appear to affect the results.

Elevation of the pericardial pressure produced uniformly a diminution of the carotid pressure. Our curves with regard to this change are similar to those previously reported by Williamson and Ets¹² and studied in greater detail by Foulger and Foulger.⁹ Pericardial pressures of 4 to 6 mm. mercury produced little or no change in systemic arterial pressure, and additional pericardial pressure caused a fall of systemic blood pressure in an increasing degree. In eighteen experiments in which the arterial pressure was allowed to fall to 30 mm. mercury or less with gradually increasing pericardial pressure, the pressure required to produce such a fall varied from 11 mm. to 28 mm., averaging 17 mm.

The pressures in the right auricle were followed in four dogs by means of a manometer filled with normal saline connected with a catheter inserted through the external jugular vein into the auricle. In two it was consistently a little less than the pericardial pressure, and in two it was a little greater. In all cases it rose as the pericardial pressure rose, and there was no change in the relationship of the auricular and pericardial pressures when the arterial pressure fell rapidly.

In the electrocardiograms diminution of amplitude of QRS as the pericardial pressure was increased was observed in twenty-seven of thirty experiments. In three it was the only change noticed. With sufficient pericardial pressure to cause the arterial pressure to fall to less than 25 mm. and to abolish pulsations in the carotid cannula QRS was usually about one-third its normal height.

The most striking changes were in the ST-segment and the T-wave. In twenty-seven of thirty experiments these changes were present. They consisted of one or more of the following phenomena: deep, sharp inversion of the T-wave in all leads; elevation of the origin of the ST-segment; depression of the origin of the ST-segment; and marked convexity of the curve following QRS with a peak nearer S than the normal T-wave. Elevation of the take-off occurred twenty-four times. It was accompanied twenty-one times by both a sharply inverted T-wave and a broad upward convexity, and three times by a broad convex peak alone. In the experiments in which both convexity of ST and inversion of T were found, the inversion of T occurred first and the inverted peak was gradually effaced, partly or wholly, as the elevation and convexity of the preceding portion of the curve increased. Except for the fact that T was occasionally inverted in Lead I while still upright in Leads II and III, changes were always in

the same direction in all leads. Depression of the ST origin, with a plateau below the isoelectric line and with a sharply inverted T-wave, was seen in two dogs. In one experiment inversion of the T-wave with no change other than diminution of the amplitude of QRS was seen. A typical example of ST and T changes is shown in Fig. 1 A. The frequency of the types of change is summarized in Table I.

TABLE I.
OCCURRENCE OF CHANGES IN PERICARDIAL EFFUSION

EXPERIMENT NO.	ELEVATION OF ST	DEPRESSION OF ST	INVERSION OF T	CONVEXITY OF ST	DIMINUTION OF QRS AMPLITUDE	REMARKS
19	+		+	+	+	
20	+		+	+	+	
21	+		+	+	+	
22 A	+		+	+	+	
22 B		+	+			
23 A	+		+	+	+	
23 B	+			+	+	
23 C	+		+	+	+	
26	+		+	+	+	
37					+	Pressure raised to 20 mm.
41 A	+		+	+	+	
41 B	+		+	+	+	
42 A			+		+	
42 B	+		+	+	+	
43	+			+	+	
44	+		+	+	+	
47					+	Pressure raised to 6 mm.
62	+		+	+	+	
63	+		+	+	+	
64	+		+	+	+	
65		+	+	+	+	
66	+		+	+	+	
80 A					+	Pressure raised to 16 mm.
80 B	+			+	+	
81 B	+		+	+	+	
81 C	+		+	+	+	
82 A	+		+	+	+	
82 B	+		+	+	+	
82 C	+		+	+	+	
111	+		+	+	+	

In one of the three dogs in which T or ST changes were not observed the pressure was not increased above 6 mm. mercury. In only two did these changes fail to appear at a pressure of 16 mm. or more, and in only four dogs did they fail to appear at 8 mm. pericardial pressure.

Release of the pericardial pressure was followed immediately in all but three dogs by a recovery of the systemic blood pressure. It frequently rose above its previous level for a time. The amplitude of the QRS complexes was also increased immediately, and the cardiac rate was slowed for a few

minutes. The changes in T and ST showed striking variations in behavior. In twelve of the twenty-seven experiments in which such changes had occurred, the deviation of ST was greater for a time after the release of the pressure than before. In three of the twelve, changes were progressively greater until the death of the dog in spite of the fact that the pressure in the pericardial cavity had been released and that the systemic blood pressure was also improved for several minutes. In one the time of maximum change was not recorded; in eight the greatest height of the convexity of ST was found from the first to the fifth minute after the pericardial pres-

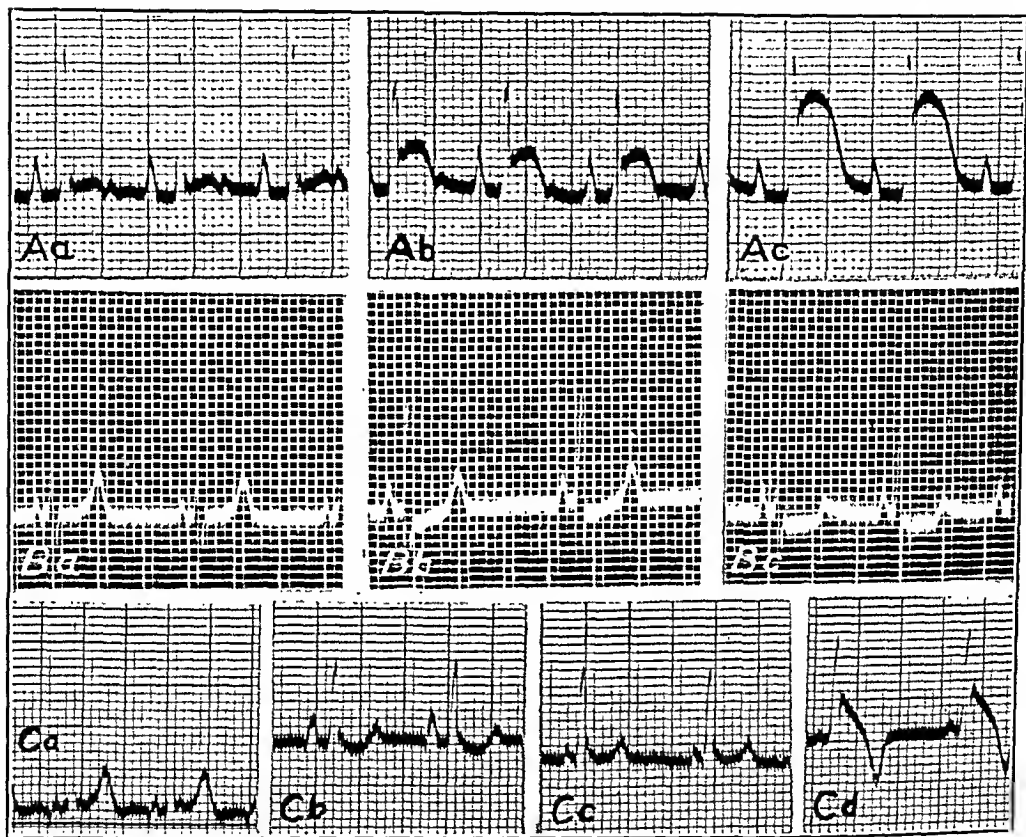


Fig. 1.—Electrocardiograms from typical experiments. All tracings are from Lead II. A, Dog with pericardial effusion: Aa, control (pericardial cannula in place); Ab, maximum change during the effusion; Ac, maximum change after the effusion. B, Dog with venae cavae ligated: Ba, control (ligatures in place but not tightened); Bb, maximum change during ligation of cavae; Bc, maximum change after ligation of cavae. C, Dog on which both experiments were performed: Ca, control (cannula and ligatures in place); Cb, maximum change during ligation of cavae; Cc, recovery; Cd, maximum change during pericardial effusion.

sure had been released. After the fifth minute all these nine showed changes approaching the normal. In fifteen experiments the first tracing taken after the release of the pericardial pressure, in each case within two minutes and usually sooner, showed that the return of the curve to normal had already begun. There was no relation that we could discover between the height of the pericardial pressure or the duration of the pressure and the behavior of the curve following release.

In three dogs the experiments were performed repeatedly with the animal lying alternately on the back and on the belly. The curves were the same regardless of the change in position.

The electrocardiographic tracings taken to control the operative procedures showed changes in the ST-segment in two dogs. There were in one case slight elevation and slight convexity of the ST-segment during the period of pneumothorax and a normal tracing after the chest had been closed. The other is illustrated in Fig. 1 A. The amplitude of QRS following the operative procedures averaged 87 per cent of its height before the chest was opened. The changes were insignificant in comparison with those obtained by increasing the pressure in the pericardium.

In considering the mechanism by which changes in the electrocardiogram with pericardial effusions are produced, at least five possibilities present themselves. These are: (1) resistance offered to venous return, either to the right or to the left side of the heart with consequent lowering of the efficiency of the coronary circulation; (2) direct pressure on the cardiac arteries or veins or on the cardiac muscle; (3) chemical action of the normal salt solution used; (4) interference with the cardiac innervation; and (5) changes in temperature. Of these we regard the first two as of most importance for further consideration. The fact that recovery occurred with the heart still bathed in the solution used for the effusion but retained in the stretched pericardium at zero pressure speaks against chemical changes. The fact that the final part of the ventricular complex is the part affected would suggest that the extrinsic cardiac nerves were not the seat of the most important changes. Changes in temperature were undoubtedly present in spite of the fact that the fluid used for effusion was warmed to body temperature, but particularly in the animals in which the chest was left open during the experiment the temperature changes must have been as great during control periods and during periods of low pericardial pressure as during the period in which the pressure was raised sufficiently to result in electrocardiographic changes.

EXPERIMENTAL OBSERVATIONS ON OCCLUSION OF THE GREAT VESSELS

To determine whether or not interference with venous return to the heart was the important factor in producing changes, experiments were devised of two general types: first, occlusion of the great vessels to see whether such changes were produced thereby in the absence of pericardial effusion; and second, supplying fluid to the heart in the presence of a pericardial effusion to see if the changes were prevented.

In the great vessel occlusion experiments the dog was anesthetized with sodium barbital and artificial respiration established. The chest was opened just to the right of the sternum and the azygos vein was ligated near its termination. Ligatures were then passed about the superior vena cava and the inferior vena cava and the ends brought out through glass tubes so that the vessels could be occluded and released at will. In some of

the experiments the pericardial sac was removed and a ligature passed in a similar fashion about the pulmonary artery at its origin. With a few exceptions in which longer periods were used, constriction of the vessels was for two minutes in each experiment, as the animal frequently failed to survive the longer periods.

In thirty-three experiments on nineteen dogs involving occlusion of the inferior and superior cavae alone the blood pressure curves resembled those of the pericardial effusion experiments. The blood pressure fell somewhat more rapidly to 10 to 20 mm. mercury, and when the vessels were released it rose immediately, usually above the previous level for a few minutes. The rise in the blood pressure was regularly accompanied by slowing of the rate.

The electrocardiographic changes were chiefly in the T-wave and in the ST-segment. The degree was much less than that noted in pericardial effusion. In no case did the changes resemble the typical cove-plane curve seen in the pericardial effusion experiments. In each of the nineteen dogs there was a slight slurring of the origin of ST with the first experiment and this usually persisted. In eleven experiments there was no other change in the ST-segment. In four experiments there was a slight elevation, and in eighteen there was a definite depression of the ST at some time during the first two minutes after the release of the vessels. These changes occurred seventeen times before the veins were released but in each case became more marked during the first or second minute after release. Inversion of the T-wave occurred four times in thirty-three experiments. T was usually more positive after the release of the vessels and frequently reached heights of 10 or 12 mm. in Leads II and III. Changes were always in the same direction in all three leads. A typical series of curves is illustrated in Fig. 1 B.

OCCLUSION OF THE PULMONARY ARTERY

Inasmuch as the pericardial effusion pressures could conceivably affect the venous return both to the left and to the right sides of the heart, it was considered desirable to observe the effects of occlusion of the pulmonary veins in order to eliminate circulation of blood through the coronary and pulmonary circuits. As this offered very great technical difficulties, it was decided to occlude the pulmonary circuit on the arterial side, thereby accomplishing what would appear to be a mechanically similar result. Seven experiments were performed on five dogs in which the great veins and the pulmonary artery were occluded simultaneously for two minutes. Seven experiments on the same five dogs were performed in which the venae cavae were occluded alone for a similar length of time. The order in which the two kinds of experiments were performed was varied without any change in the results. In each of the experiments of this series, when the venae cavae were occluded alone, there was a slight depression of the ST-segment which became more marked when the vessels were released. The maximum deviation from the isoelectric line averaged 2.1 mm. and occurred uni-

formly during the first minute after release. When the pulmonary artery was ligated also, the changes were exactly the same, but of greater degree; the maximum deviation of ST averaged 3.0 mm. and occurred during the first minute after release in six experiments and during the second minute in one.

In five dogs both artificial pericardial effusion and occlusion of the veins were performed. With pericardial effusion both marked elevation of ST and inversion of T occurred in four and inversion of T with a convex ST approximately on the base line in the fifth. With occlusion of the veins the only marked change was increased height of the T-wave in four. The ST-segment deviated slightly upward in two and downward in two and was unchanged in one. The different types of curve obtained in the same dog are illustrated in Fig. 1 C.

In seven experiments the pericardial effusion was produced in the customary fashion and the ST changes described above were obtained. Following a recovery period the experiment was repeated, but at the same time physiological solution of sodium chloride was allowed to flow into the right auricle through a catheter inserted into the external jugular vein. The rate of flow was from 100 to 200 c.c. a minute. In these experiments the blood pressure fell slightly, but much less than when no infusion was given. The electrocardiographic changes were equally great in two, more marked in two, and less in three than in the ordinary pericardial effusion experiment. In none were ST and T changes prevented.

In four experiments a similar infusion was given into the left auricle through a special cannula which was inserted into the auricular appendage through a hole in the pericardium which was made water-tight by a purse string and nut about the cannula. In all of this series inverted T-waves were produced, and in three animals there was an elevation of the ST-segment. The electrocardiographic changes were the same in each animal with and without the infusion of fluid into the auricle, although the fall in blood pressure was less when the infusion was given simultaneously with the pericardial effusion.

It is evident from these experiments that elevation of the ST-segment of the electrocardiogram of the dog in the presence of pericardial effusion is not simply a function of the interference with venous return to the right side or to both sides of the heart. Interference with the venous return alone appears to have little effect on the ST-segment, but tends to produce changes in the opposite direction to those seen in pericardial effusions. Sudden filling of the heart, as when the occluded vessels are released, produces changes opposite in direction to those seen in pericardial effusion. Katz and Wallace¹³ have produced evidence to indicate that fall in blood pressure contributes to the mechanism of ST changes in coronary occlusion, and while the general embarrassment of circulation may be a contributory factor here, we believe that it is necessary to assume some local action also, presumably compression of the cardiac muscle or of its vessels.

SUMMARY

The electrocardiographic and blood pressure changes previously reported in the presence of artificial pericardial effusions have been confirmed with some additional detail, particularly concerning the recovery period. Change in position of the animal does not alter the extent or direction of the observed changes. Simultaneous rapid infusion of normal saline solution into the right or left auricle modifies the blood pressure changes, but not the electrocardiographic changes. Transient occlusion of the venae cavae or of the cavae and the pulmonary artery causes a comparable drop in systemic blood pressure, but does not reproduce the electrocardiographic changes of artificial pericardial effusion, and tends to produce changes less in degree and opposite in direction. This difference holds whether the experiments are performed on the same or on different animals. Some possible mechanisms by which pericardial effusion might produce electrocardiographic change are discussed and interference with venous return, chemical changes, and temperature changes eliminated from consideration as the primary mechanism. The effect of direct pressure on the myocardium, on the coronary vessels, and on the Thebesian vessels remains as an important possibility.

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A SIMPLE METHOD FOR GRAPHIC DESCRIPTION OF CARDIAC AUSCULTATORY SIGNS*

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PHYSICIANS who are in the habit of recording their clinical observations are familiar with the sense of lack of completeness which they experience in describing cardiac auscultatory signs. One factor which contributes to this feeling of dissatisfaction is that in writing the record after the entire physical examination has been completed, there is an appreciable degree of uncertainty as to whether one's memory of the signs at various points over the precordium is exact. A second factor is that in order to describe the signs heard at all points, the report must be rather long, and one rarely escapes the feeling of tediousness both in writing and in reading it. Thus the record, if complete, is verbose, and if brief, is incomplete. By using the graphic method described below the memory factor is eliminated because the record is made while listening; and the signs can be accurately described without the use of any words in most instances, and only an occasional adjective to describe some peculiar quality of a sound or murmur in some cases.

\uparrow Longitudinal axis = *Loudness*.
 \longrightarrow Transverse axis = *Duration*.

1 cm = 0.20 second.

mmm = *Low pitched, coarse or rumbling murmur.*

 = High pitched, blowing or whiffy murmur.



Normal heart sounds.
One cycle.

Fig. 1.—The code of symbols and rules for the graphic description of cardiac sounds and murmurs.

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The essential features of a heart sound may be expressed in terms of its relative loudness and duration; thus a loud, short sound has a sharp, snapping quality and a less loud, longer sound has a duller quality. By representing loudness in terms of the vertical axis and duration by the horizontal axis a rectangular figure describing the heart sound is drawn. It is obviously necessary to adopt some general rules for guidance in determining first, the size of the rectangles and second, the length of the spaces between them which denote time intervals. As the standard size of average

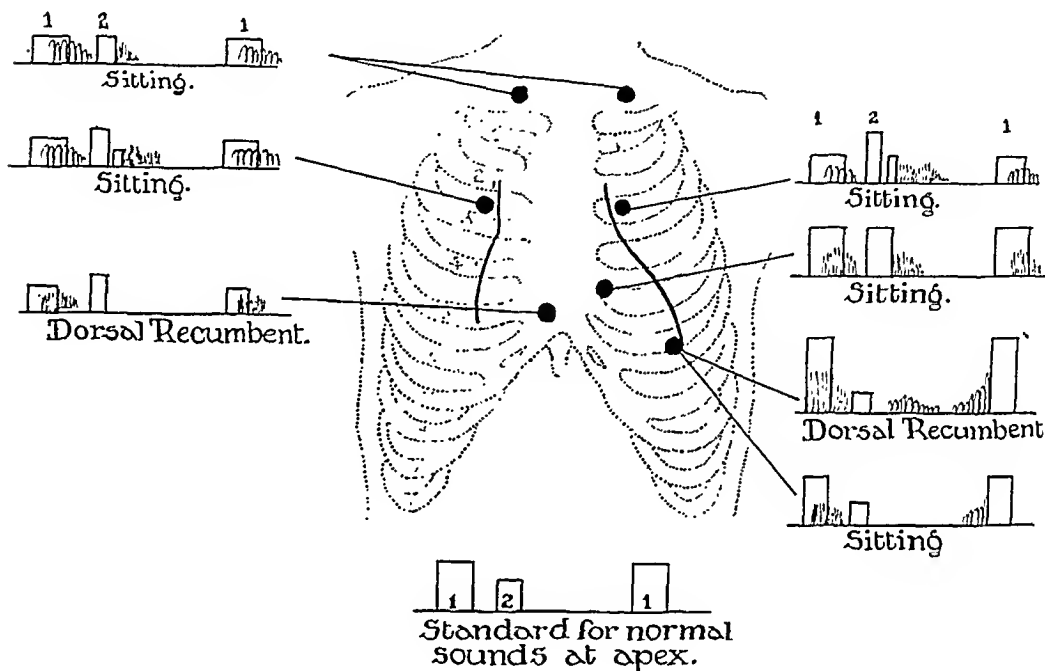


Fig. 2.—The auscultatory signs observed in a case of rheumatic heart disease with aortic stenosis and insufficiency and mitral stenosis and insufficiency. The practical value of the graphic method, its accuracy and effectiveness as a time-saving procedure are well illustrated by comparing the above record, the original of which was made as the observer was listening over the heart, with the following verbal description.

At the apex: the first sound is loud and sharp and accompanied by a blowing systolic murmur which continues almost up to the second sound; both the sound and the murmur are louder in the dorsal recumbent than in the sitting posture; the second sound is rather faint. In the sitting posture a short presystolic, rough crescendo murmur is heard. In the dorsal recumbent posture, a rumbling mid-diastolic decrescendo murmur and loud, rough, presystolic murmur are heard; the latter is longer than in the sitting posture. At the left border of sternum, in the fourth space, the first and second sounds are moderately loud, the second is sharper than the first; a late systolic blowing murmur accompanies and follows the first sound, and a blowing diastolic murmur of about equal loudness follows the second sound without any interval between the end of the sound and the beginning of the murmur. At the pulmonic area the first sound is less loud than at the apex and is accompanied by a moderately loud, somewhat late, rough systolic murmur; the second is duplicated, the first half being louder than the second half and also louder than the first sound; a blowing decrescendo diastolic follows immediately after the second half of the second sound. At the aortic area, the first sound and systolic murmur are similar but somewhat louder than at pulmonic area; the second is duplicated but less loud than at pulmonic area, and the diastolic murmur seems similar in all respects. In the neck region, above the clavicle, the sounds and murmurs are about as at the aortic area, except that the second sound is not duplicated. At the tricuspid area, both sounds are less loud than anywhere else over precordium, and there is only a relatively short, late blowing systolic murmur.

normal sounds, 10 mm. (vertical) by 7 mm. (horizontal), for the first sound, and 7 mm. by 5 mm. for the second, are convenient and suitable. The time is expressed in terms of 1 cm. for 0.20 second. By describing the

first and second sounds of one cycle and the first sound of the next, one indicates the nature of the heart rate, and the length of systolic and diastolic periods is clearly portrayed. If the rhythm is normal, only one cardiac cycle need be described (Fig. 1); variations in rhythm may be described by recording a series of sounds in the order in which they are heard. The relative loudness and duration of the sounds are expressed by varying the size and shape of rectangles. Holding the stethoscope with one hand the graphic notes are made with the other, while listening.

The point at which the signs are observed can be accurately recorded with the aid of a simple diagram of the heart. I have tried using the

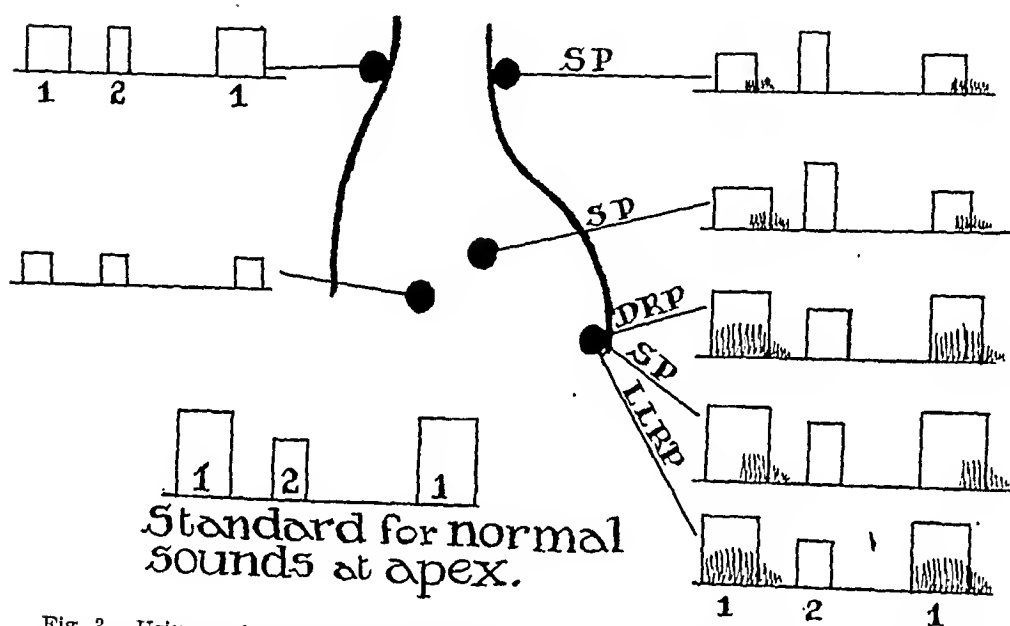


Fig. 3.—Using a simple diagram of the heart, without an outline of the thorax, the points at which the stethoscope is applied may be satisfactorily indicated. The relative loudness of the sounds, the loudness, duration and time relations of the blowing systolic murmur at various points over the precordium are portrayed. S.P. = sitting posture; D.R.P. = dorsal recumbent posture. L.L.R.P. = left lateral recumbent posture.

orthodiagraphic chart of the heart in its actual size for recording the signs graphically at the very points where the stethoscope was applied, but have found it less simple and convenient than the method shown in Figs. 2 and 3, which requires only the ordinary notepaper, preferably with an outline of the thorax stamped on it.

The essential features of a heart murmur are: first, its time relations to the heart sounds; second, its pitch; third, its loudness; fourth, its duration; and last, the point, or points, at which it is heard. The pattern of a single cardiac cycle (Fig. 2) offers a convenient plan for recording accurately the portion of the cycle during which a murmur is heard; thus its time relations to the sounds and its duration are readily indicated. The pitch of a murmur is either high or low, depending on the dominant vibration frequency of its sound waves. Thus low-pitched murmurs may be described by a series of rather widely separated vertical lines joined by

curves, forming a serrated border (Fig. 1) to indicate the dominance of low vibration frequencies. In the presence of a sufficiently loud low-pitched murmur a thrill is palpable; the serrated border of the diagram representing the low-pitched murmur suggests the tactile sensation of a thrill. High-pitched murmurs are represented by closely placed vertical lines to indicate higher vibration frequency. The loudness of the murmur is conveniently described by varying the vertical length of the lines, the description of the loudness of the heart sounds being used as a standard for comparison. The points at which the murmur is heard are readily indicated by referring to a diagram of the heart as in Fig. 2 or Fig. 3.

AORTIC ANEURYSM WITH HUGE SECONDARY ANEURYSM OF THE CHEST WALL. REPORT OF A CASE

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A THIN colored laborer, thirty-two years of age, entered Cook County Hospital, February 5, 1932, complaining of substernal "soreness," pain in the left shoulder and chest, productive cough, loss of 15 pounds in weight, and dyspnea on slight exertion. The initial symptom, substernal discomfort, had been present for one year. He had had gonorrhea twice and a chancre at the age of twenty years, for which he received forty-eight mercury inunctions. He had drunk one-half pint of whiskey daily for ten years. The family history was not remarkable.

On the first examination there was a small pulsating mass at the right sternoclavicular articulation over which a systolic thrill could be palpated. There was extensive widening of mediastinal dullness (15 cm.) The heart was enlarged slightly to the left (11 cm. from the midsternal line). A systolic murmur at the base and booming aortic second sound also were present. Other findings were: Hyperresonance over the apex of the right lung anteriorly and hyporesonance over the same portion posteriorly; decrease in Kronig's isthmus on the left side; extension of hilar dullness laterally 6 cm. from the spine on the right side; enlarged, tender prostate; carious teeth and slightly enlarged lymph nodes in the right supraclavicular fossa. The blood pressure of the right arm was 100/74, of the left arm 110/84, pulse rate 104, temperature 98.6 degrees. Wassermann tests of blood serum and spinal fluid were negative. The erythrocyte count was 4,200,000, hemoglobin 78 per cent, and leucocytes 10,500. The urinalysis was negative except for an occasional hyalin cast. The electrocardiogram showed a sinus mechanism, normal conduction time and a prominent Q-wave in Leads II and III. X-ray and fluoroscopic examinations revealed a large aneurysm involving the aorta, with marked opacity in the middle half of the right lung.

He was given bismuth salicylate intramuscularly for one month. March 14 he left the hospital without permission.

The patient returned June 6, 1932, complaining of shortness of breath, numbness of the right hand and arm and a large swelling of the right chest.

Examination now showed a large tender mass, extending from the right infraclavicular area to about the third intercostal space, which had an expansile pulsation synchronous with the heart beat. The blood pressure

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in the right arm was 110/90 and in the left arm 120/90. There were no other changes in the physical findings. The erythrocyte count had dropped to 3,400,000 and the hemoglobin to 60 per cent. The electrocardiogram was not changed. The condition of the patient rapidly became worse. He experienced a moderate amount of pain which was readily relieved by morphine. The size of the mass increased rapidly so that on June 18 it measured 12 by 20 cm. and was 10 cm. in height. It became more tender, and three days before death blood began to ooze through the skin. An electrocardiogram made on this date showed a marked decrease in voltage in all leads, especially the first. June 24 the patient fell out of bed, with no demonstrable bad effects. He became more and more dyspneic and died June 26.



Fig. 1.

Fig. 2.

Fig. 1.—Front view of patient taken June 20.

Fig. 2.—Side view of patient. Same date as in Fig. 1.

A necropsy showed a bulging mass of the right chest which measured 15 by 24 by 25 cm. The veins of the chest were dilated, and the skin overlying the swelling was thin and hemorrhagic. The mass was a huge sac-like structure formed by the muscles and fascia of the chest, and filled with laminated blood clot. The sac communicated with a similar cavity in the right pleural cavity by a tract between the second and third ribs. These ribs were separated widely and partially eroded. The sac in the pleural cavity was continuous with a large fusiform aneurysm involving the entire arch of the aorta. The heart was moderately enlarged. The myocardium was purple gray in color and friable. Immediately above the aortic valve was a fusiform dilatation of the aorta involving the entire arch, forming an aneurysm about 14 cm. in diameter filled with laminated

blood clot. The entire intima of the aorta was wrinkled and puckered with scars. The body of the fourth dorsal vertebra was eroded.

The anatomical diagnosis was:

Fusiform aneurysm of the arch of the aorta, eroding through the right chest wall with secondary aneurysm formed by the chest wall; syphilitic aortitis; fatty infiltration of the liver; parenchymatous degeneration of



Fig. 3.—X-ray picture of chest taken June 7.

the myocardium; chronic tumor of the spleen; decreased lipoid content of the adrenals and marked passive congestion of the kidneys.

COMMENT

A report is made of a fusiform aneurysm of the aorta with an enormous secondary aneurysm of the chest wall.

Despite the size and character of the aneurysm, rupture did not occur because of the laminated clot within the sac. Death was the result of cardiac exhaustion.

Department of Clinical Reports

THE REMOVAL OF A LARGE NEEDLE FROM THE HEART WITH ELECTROCARDIOGRAPHIC CHANGES IN RHYTHM DURING OPERATION*

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THE removal of foreign bodies from various situations in the heart is recorded from time to time. These have included needles, nails and particularly during the war, bullets, and other foreign bodies. Of the cases reported, the needle has not infrequently been mentioned and, when penetrating deeply, has, in many cases, been followed by death. Hinton¹ reported one and quotes Meyer-Pantin² who collected twelve such cases.

Apart from those cases in which death is an early event, it is remarkable how some patients will tolerate a large foreign body apparently for a considerable length of time. Occasionally a foreign body, corroded and friable, has been found incidentally at autopsy, and its appearance has suggested that it has been retained for a number of years.

The patients who survive its entry generally develop symptoms which gradually increase in severity. Intense precordial pain and dyspnea have been frequently noted, and in one case reported³ irregularity of the pulse and tachycardia supervened.

CASE REPORT

A case which came to our attention was that of a girl, twenty-two years of age, who was referred to this hospital in the surgical service of Dr. F. A. C. Scrimger. Her complaints were those of severe pain over the precordium, radiating over the front of the chest; weakness, and dyspnea on exertion.

Her history was that five months previously, while employed as a domestic, she fell to the floor while doing her housework. In falling, a needle which she had stuck in the front of her dress, was driven into the wall of her left chest. It was, at the time, quite painful but she did not immediately seek medical advice. The needle apparently disappeared completely from sight and no attempt was made to recover it. During the ensuing weeks she became increasingly troubled with pain in the chest. It was described as sharp and severe, but never of a stabbing character. It gradually became persistent and was constantly present, day and night. At times it radiated across the front of the chest from a point of maximum intensity over the precordial region. It did not radiate down either arm, or to the back. It was not associated with faintness or loss of consciousness. The pain was greatly increased by movements of her arms and for sometime past she had been unable to work. Four weeks previous to admission the pain became so severe that she was completely in-

*From the McGill University Clinic, Royal Victoria Hospital. The surgical aspect of the case is being reported elsewhere by Dr. Scrimger.

capacitated and was forced to consult a physician. At this time she began to experience some difficulty in breathing, a condition which added greatly to her disability. An x-ray film disclosed a needle-like shadow within the cardiac area, and she was referred by Dr. A. V. Traynor of Kitchener, Ont., to the Royal Victoria Hospital.

Her personal history revealed that she was born in Ukraina, that there had never been any cardiac symptoms prior to the present illness and that there was no history of previous illness.

The patient was well developed, and, except in the cardiovascular system, examination revealed nothing of importance. The pulse was regular; there was no evidence of arterial thickening, and the blood pressure was 130 mm. Hg systolic and



Fig. 1.—Needle 7 cm. in length lying within the heart. The point is at B. The pericardial adhesion is at C.

94 mm. Hg diastolic. There was no evidence of increase in venous pressure. The heart was slightly enlarged to the left. The sounds were regular, and of normal intensity. There were no murmurs present. There was no pericardial friction rub or evidence of increase in fluid in the pericardial cavity. The lungs were clear. The liver and spleen were not enlarged. There was no peripheral edema. The urine was normal. The leucocyte count was 6,400. The temperature was normal and remained so until operation.

A combined fluoroscopic and stereoscopic examination revealed a large needle lying within the cardiac shadow about midway between the sternum and vertebral column and pointing obliquely posterior. There was marked oscillation of the needle of about one inch with each cardiac contraction. The needle was judged to have penetrated the anterior surface of the left ventricle and, pointing posteriorly, to be lying within the cavity or myocardium of the left ventricle. Fig. 1 is an x-ray pic-

ture of the heart showing the position of the needle in an A-P view. The point of the needle, as later determined, is at *B*. The pericardial adhesion was at point *C*.

The electrocardiogram (Fig. 2) taken on admission shows a low voltage of the QRS deflections with an acutely negative T deflection in the second and third leads. This was taken as evidence of localized ventricular muscle damage. The electrocardiogram resembles that seen in coronary thrombosis of some duration.

The operation by Dr. Scrimger, reported in detail elsewhere, was as follows:

An incision was made from the level of the second rib in the midsternal line downward to the xiphoid and then across to the left parallel to the rib margins three inches beyond the tip of the xiphoid. The sternum was then chiselled through about its midpoint from the xiphoid to the level of the second rib. The chisel was then turned and the sternum cut through into the second rib and the cartilage of the second rib cut with the knife, thus making an osteoplastic flap which exposed the anterior

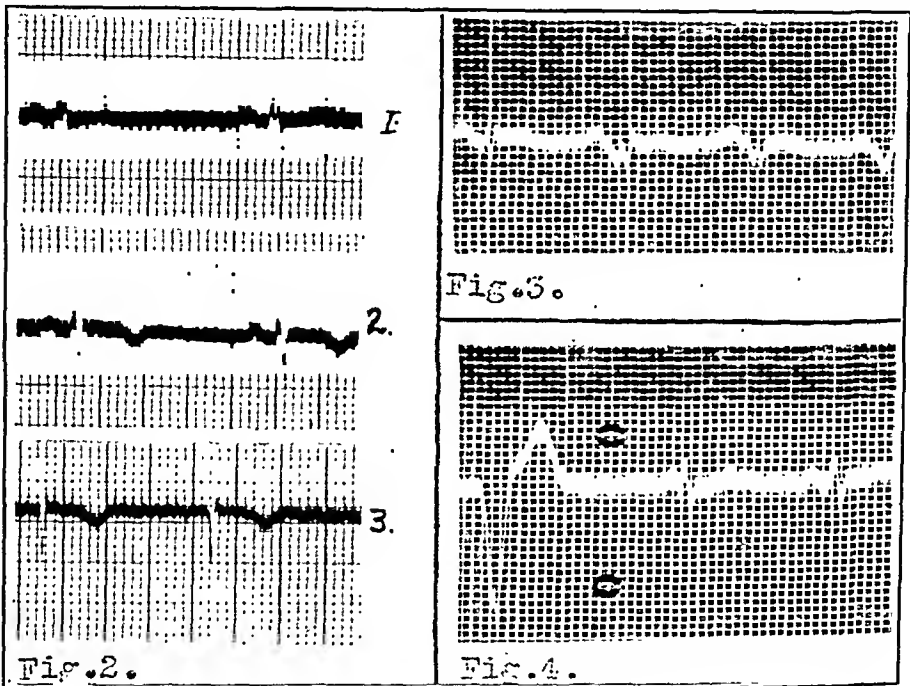


Fig. 2.—Tracing taken before operation. A low voltage of the QRS deflections and negative T deflections in the second and third leads may be observed.

Figs. 3 and 4.—A period of lowered voltage with occasional extrasystoles on inserting the hand into the pericardial cavity was followed by a change in the QRS deflections (Fig. 3). Fig. 4 follows shortly after with a return to the previous QRS formation. The hand of the operator was in the pericardial cavity with the palm on the posterior surface of the heart. (Lead II.)

mediastinum. The pleura was pushed away toward the left until a good exposure of the anterior mediastinum was obtained. The pericardium was then opened.

During chiselling of the sternum, no change in the electrocardiogram was observed. On opening the pericardial sac, there was a decrease in voltage of the QRS and T deflections.

A normal amount of pericardial fluid was found and the heart was exposed, beating regularly. The heart was covered with fat on the surface. On exploring the pericardium with the finger, no sign of the needle could be found. This manoeuvre elicited left and right ventricular extrasystoles, which in turn were followed by a regular rhythm.

The only deformity was a band of rather firm, fibrous adhesions about three-fourths of an inch broad extending from the inferior surface of the left ventricle to

the pericardial wall. This was hooked with the finger and brought forward into view and cut.

This manipulation in the pericardial cavity was accompanied by a marked change in the electrocardiogram. A marked notching of the QRS deflections was observed, later followed by one left ventricular extrasystole and a return to normal deflections. (Figs. 3 and 4.)

The hand was introduced around the heart, feeling toward the base among the roots of the great vessels. This could only be carried on for a matter of a few minutes at a time and if prolonged resulted in marked pallor and disappearance of the pulse together with changes in the pupils, sometimes dilatation and sometimes contraction. After several such attempts, a portion of the needle was recognized as projecting from the posterior surface of the heart about three-fourths of an inch into the pericardial cavity.

At this point a prominent S-wave in the electrocardiogram was replaced by a prominent and notched R deflection which was followed by alternate right and left

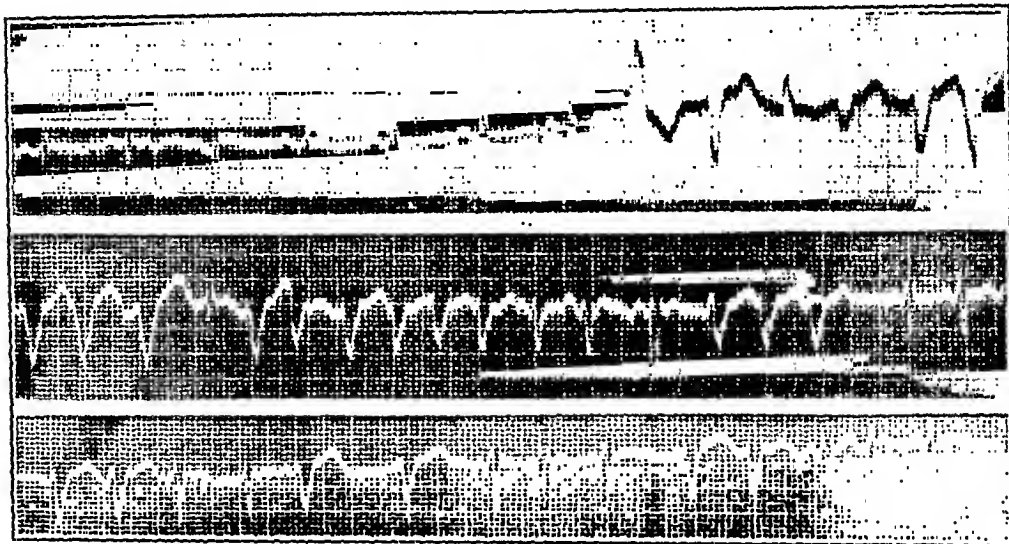


Fig. 5. The tracing is a continuous one taken when the operator's hand was in contact with the needle. In the first part a change in form of the QRS deflections is seen followed by alternate right and left ventricular extrasystoles and a ventricular rhythm interrupted by an occasional supraventricular beat. In the last part a return to the normal is seen. The tracing is Lead II.

ventricular extrasystoles and then a ventricular rhythm interrupted by an occasional supraventricular beat. The heart then returned to a normal rhythm. (Fig. 5.)

This free portion of the needle was situated among the great vessels at the base of the heart. The needle in this situation was not free, but there was some soft tissue between the finger and the needle. After several attempts to feel it, it was recognized that the needle lay in an oblique position extending downward and to the left and lay mostly in the substance, or in the cavity of the left ventricle. As it seemed too dangerous to attempt to withdraw the needle by grasping the exposed portion, the thumb of the right hand was placed on the exposed portion of the needle posteriorly, and the heart being grasped between the fingers of the hand, the needle was thrust forward in the line of its axis until the point appeared through the anterior wall of the ventricle for about one-half an inch. The point of the needle corresponded fairly closely to the situation of the adhesions which had previously been released. At this point the pulse disappeared and the patient stopped breathing.

The appearance of occasional runs of ventricular tachycardia continued until the operator's hand was in contact with the needle and was attempting to dislodge it.

At this point there developed an irregular rhythm of right ventricular origin which changed to one of left ventricular origin. (Fig. 6.) This rhythm was irregular and seemed not far removed from ventricular fibrillation. This coincided with the disappearance of the pulse and cessation of respiration. The heart then returned to a normal rhythm.

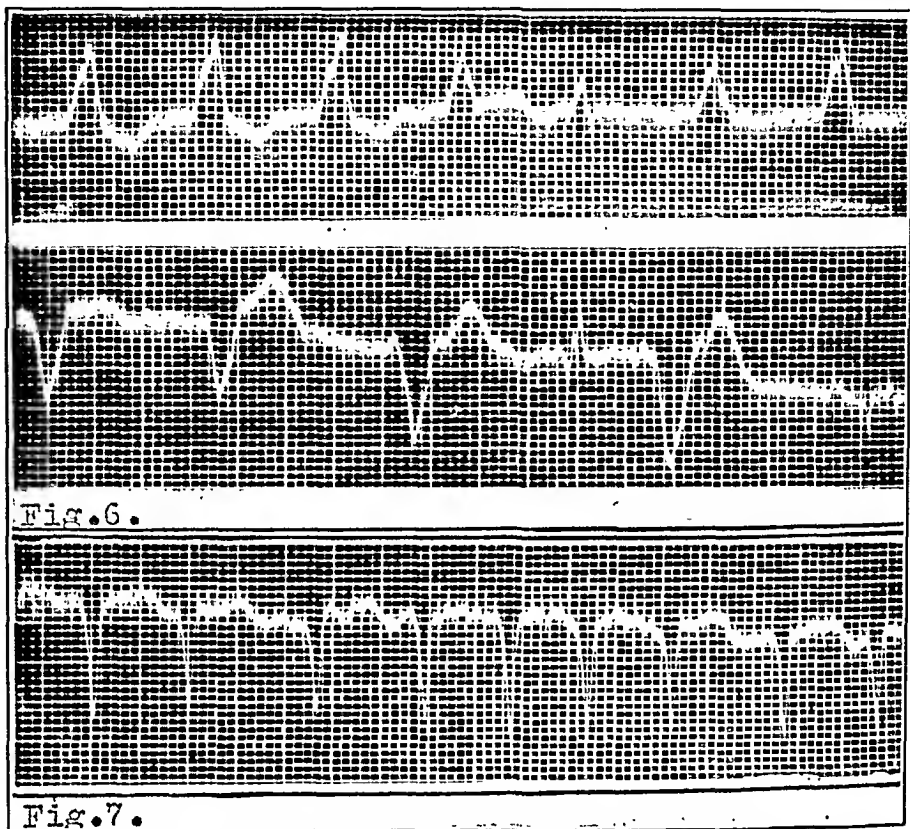


Fig. 6.—Portion of a continuous tracing taken when the operator was attempting to dislodge the needle. A rhythm of right ventricular origin changed to one of left ventricular origin. The average rate is 81 per minute. (Lead II.)

Fig. 7.—Ventricular tachycardia, rate 138 per minute. Taken when the operator was forcing the needle through the wall of the left ventricle. (Lead II.)

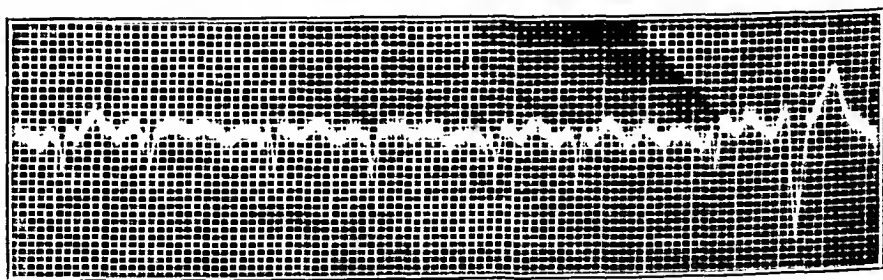


Fig. 8.—Lead II taken immediately following Fig. 7. Auricular flutter with left ventricular extrasystole. This was followed by short runs of ventricular tachycardia.

The heart, therefore, had to be released from the grasp of the hand. As soon as this was done, and this had to be repeated four or five times with the same result, the heart took up its rhythm again; the pulse re-appeared and the color improved. At no time, however, did the pulsation of the heart cease or the muscle lose its tone. On the third attempt, the portion of the needle which projected from the wall of the ventricle was grasped between the first and second fingers of the hand inside the pericardium and gradually withdrawn through the heart and removed.

Just prior to grasping the needle, the rhythm had again returned to normal, when on grasping the needle and forcing it through the heart (left ventricle) a continuous ventricular tachycardia, rate 138 per minute developed. The tachycardia was left ventricular in origin. (Fig. 7.) As the needle was removed this, in turn, was succeeded by an auricular flutter interrupted by an occasional left ventricular extrasystole. (Fig. 8.) The rhythm then returned to normal.

There was a small amount of bleeding into the pericardium, but nothing alarming. After waiting some time to allow the heart to recover its rhythm and the pulse and color to improve, the pericardium was closed with continuous suture. The sternum was then replaced and sutured into position. The wound was closed without any drainage. At no time was the pleura opened. The patient left the table in good condition, color satisfactory, pulse about 90 and blood pressure 120/70.

The electrocardiogram (Fig. 9) taken just before leaving the operating table showed a regular rhythm; rate 90 per minute. The voltage was somewhat lower than before operation. The needle removed was of the "darning needle" type and measured 7 cm. in length. It lay obliquely, postero-anteriorly, about three-fourths of an inch of the "head" protruding from the right auricle into the pericardial cavity posteriorly at the root of the great vessels. The body of the needle lay in the myocardium of the left ventricle, the "point" directed latterly. Whether a portion of the body of the needle lay within the cavity of the left ventricle, could not be accurately determined. The needle had blood crusts on the surface but showed no signs of corrosion. The needle after penetrating the chest wall had evidently penetrated the anterior wall of the right ventricle or auricle and had been pulled into the position described.

The operation was performed on June 17, 1932. The following day, June 18, the pulse averaged about 120 per minute. Temperature 99° F., blood pressure 110/80. The electrocardiogram (Fig. 10) showed an increase in the voltage of the QRS deflections and an elevation of the R-T interval in Leads I and II, a tracing resembling that of an acute coronary occlusion. She complained of severe pain in the region of the sternum and some respiratory distress. Three hundred cubic centimeters of a 20 per cent glucose saline solution was given intravenously.

On June 21 she was very restless, and the respirations had increased to 40 per minute. The temperature was 100° F. and the pulse was 120 per minute. The blood pressure was unchanged. There was a suggestion of a small amount of fluid in the pericardial cavity. At the base of the left lung there was a small area of consolidation similar to that frequently seen in acute pericarditis. The electrocardiogram showed the elevation of the R-T interval in Leads I and II slightly more marked. The possibility that this might be due to the pericardial effusion, though moderate, as suggested by Scott, Feil and Katz⁴ was considered. It was thought more probable, however, that it was due to the recent damage to the ventricle on removing the needle.

During the next few days the blood pressure decreased slightly, averaging about 98/68. On June 27, the blood pressure was 102/65. Temperature 100.4°. The lungs were now clear. The electrocardiogram had changed (Fig. 11); the T deflection in Lead I showing an upward convexity, later becoming negative; it was diphasic in Lead II and isoelectric in Lead III. There was also some decrease in voltage of the QRS deflections.

On June 30 the temperature was normal and remained so. On July 2 she was up in a wheel chair, and on July 5 she was walking about the ward. On July 7 the electrocardiogram showed a negative T deflection in all leads together with a low voltage of the QRS deflections. (Fig. 12.) She was discharged from the hospital on July 8, free from all symptoms. Examination showed slight enlargement of the heart. There were no murmurs present.

She returned to the hospital for an electrocardiogram on July 20 (Fig. 13). The

T deflection was now upright in Lead I. On August 3 the T deflection had become upright in Leads I and II but remained negative in Lead III. This might be taken as evidence of improvement over the tracing taken before operation, (Fig. 2). In

Fig. 9.

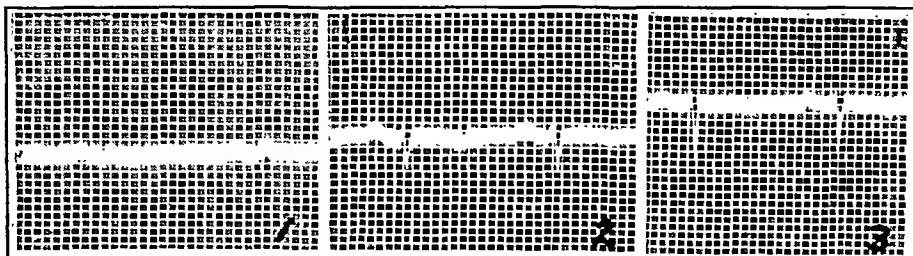


Fig. 10.

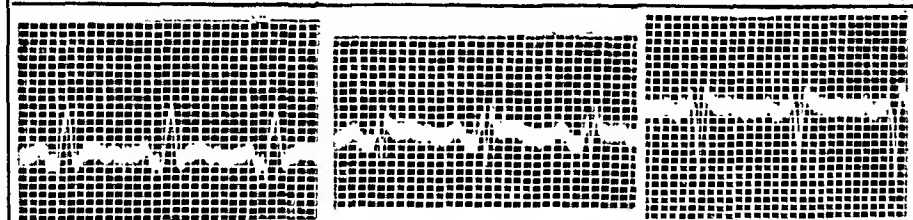


Fig. 11.

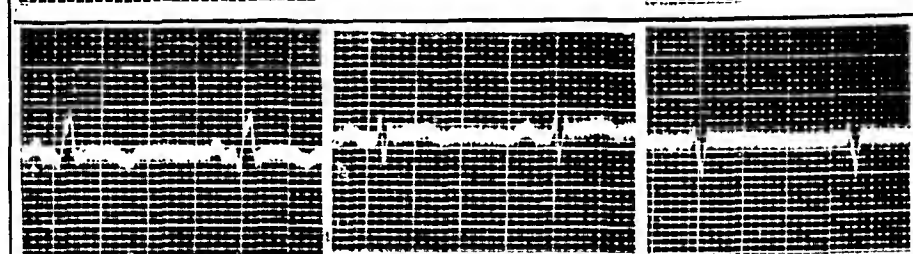


Fig. 12.

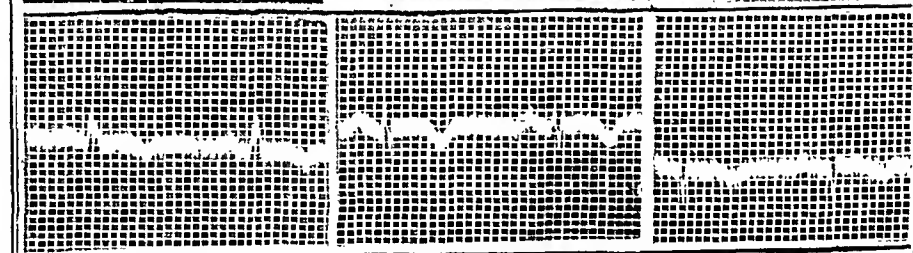


Fig. 13.

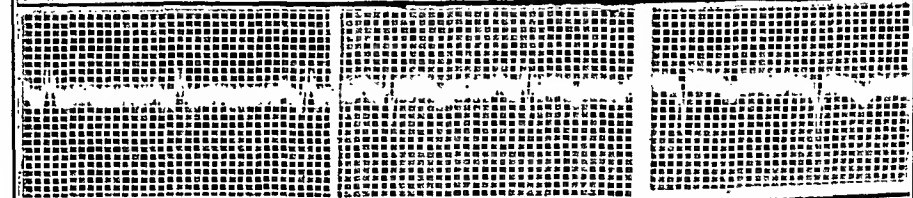


Fig. 14.

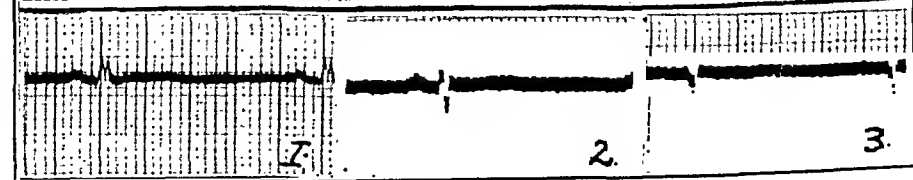


Fig. 9.—Electrocardiogram taken just before leaving the operating table. The voltage was somewhat lower than that before operation.

Figs. 10 to 14.—Progressive changes in the electrocardiogram taken at subsequent dates after the operation, which was performed June 17. Fig. 10, June 18; Fig. 11, June 27; Fig. 12, July 7; Fig. 13, July 20; Fig. 14, December 9.

the latter the T deflection in Lead I was of low voltage, and was acutely negative in Lead II. She returned for examination on December 9. In the interval she had been entirely free from symptoms and had returned to work. The electrocardiogram is shown in Fig. 14.

Selected Abstracts

Hyman, Albert S.: Resuscitation of the Stopped Heart in Intracardial Therapy.

II. Experimental Use of an Artificial Pacemaker. Arch. Int. Med. 50: 283, 1932.

Stimulation of the stopped heart by electrical methods has previously failed because most investigators have attempted to reactivate the heart by neurogenic excitation.

When electric current has been applied directly to the heart, it has been done by placing the entire organ in the electric circuit; the result has been that the heart is unable to maintain its normal cycle. When strong currents have been used, the factors discovered in electrocution are seen to be present.

In using a clinical needle through which is carried an electric impulse, and in having the two electrodes so close together that only a small pathway is concerned in the electric arc established by the heart muscle, an irritable point is produced.

This irritable point becomes the focus from which an excitation wave may spread over the heart muscle, the excitation wave developing and spreading according to normal physiological conditions. The impulse released from the pacemaker needle differs in no way from that produced by the prick of an injecting needle except that in the latter instance only one stimulus is developed, while in the former any number can be delivered to the heart muscle.

An apparatus has been constructed which attempts to simulate the excitation wave developed by the normal sinus nodal pacemaker; it consists of a special current generated by a magneto which is activated by a spring motor, making it instantaneously available at any time, at any place and under all circumstances, as it is an independent electric unit. The current from this generator can be so regulated that the impulses are delivered to the needle point at a constant regular rate varying from 30 to 120 beats per minute.

The needles are carried in hermetically sealed tubes that have been sterilized; in the puncture procedure the same aseptic precautions must be observed as in any other sterile injecting manipulation. The needle is inserted into an insulated handle which carries the terminals of the electric circuit from the generator. A convenient switch on the handle permits the current to be introduced into the needle at will.

Experimental animal studies have shown that the arrested heart is rapidly returned to automatic sinus activity after the response to the artificial pacemaker has restored some of the normal circulatory balance. Typical graphs are presented which show the electrocardiographic exposition of the events that take place in the heart when the artificial pacemaker is applied to the stopped heart.

The use of the artificial pacemaker in the normally beating heart is also shown, and the relative harmlessness of the procedure is indicated, the result being the development of a regular extrasystolic arrhythmia. The artificial pacemaker impulse is followed by an ectopic beat from that area of the heart stimulated.

The question of utilizing the artificial pacemaker in certain gross irregularities of the heart is also discussed, but this field still requires considerable investigation before conclusions of any type can be considered.

In view of the possible advantageous results to be anticipated by the use of the artificial pacemaker in the arrested heart which does not respond to the usual methods of therapy, the employment of this method is suggested. When patients have succumbed to disease processes, an attempt can be made to renew automatic cardiac activity by the use of the artificial pacemaker without in any way jeopardizing their condition.

When correctly used, the artificial pacemaker may prove to be of inestimable value in the restoration of those patients now succumbing to cardiac arrest; employed together with other established life-saving procedures it may well be included in every physician's armamentarium against the final struggle with death.

Hooker, D. R., Kouwenhoven, W. B., and Langworthy, O. R.: The Effect of Alternating Electrical Current on the Heart. *Am. J. Phys.* 103: 444, 1933.

Working with the dog heart in fully anesthetized animals, the authors have studied the effects produced by different values of 60 cycle alternating current. This was used because of the ease with which permanent ventricular fibrillation may be established by electrical stimulation and because the main interest was to investigate the value of electric countershock in overcoming ventricular fibrillation. Alternating currents of five or more amperes when passed through the body for one-half to five seconds will not produce ventricular fibrillation. However, the usual house circuit of 110 volts similarly applied will invariably produce fibrillation because the current that flows presumably is not sufficient to inhibit the heart. One milliamperere of current applied directly to the ventricular musculature is sufficient to cause fibrillation, and the extreme ventricular apex is as sensitive as any other point on the ventricles.

With the electrodes applied directly to the heart, currents of 0.4 ampere for five seconds will cause fibrillation and currents of 0.8 ampere or more will stop fibrillation. A current of 0.8 ampere will not induce fibrillation, and a current of 0.45 ampere will not stop fibrillation. In the intact animal with the electrodes on either side of the thorax, the current spreads out over the body tissues. In order to obtain a sufficient current through the heart to arrest fibrillation, the countershock current must be increased to a value of at least four or five amperes.

Following the countershock, the ventricles are quiescent for a brief period. When contractions began they were very feeble but quickly increased in vigor, and the circulation was re-established if fibrillation has not continued for long. If fibrillation has lasted for two minutes or more, spontaneous recovery of effective beats will not follow. Under these circumstances, cardiac massage may be of signal benefit.

Of even greater assistance than cardiac massage is the central carotid injection of adrenalin in a salt solution. Best results were obtained by injecting under a pressure of 150 mm. of mercury from 5 c.c. to 10 c.c. per pound of a solution made up of calcium chloride 0.046 per cent in sodium chloride 0.9 per cent containing heparin, saturated with oxygen and warmed to body temperature. To this mixture 2 c.c. adrenalin chloride 1:1000 should be added.

Stewart, Harold J., and Cohn, Alfred E.: Studies on the Effect of the Action of Digitalis on the Output of Blood From the Heart. II. The Effect on the Output of the Hearts of Dogs Subject to Artificial Auricular Fibrillation. *J. Clin. Investigation* 11: 897, 1932.

During auricular fibrillation when the ventricular rate is rapid, the cardiac output per minute is less than it is during the normal slower sinus rhythm. In consequence of this abnormal rhythm in intact unanesthetized trained dogs, the heart increases in size. This conclusion is based on a larger number of observations than was possible in an earlier paper. When the cardiac output is diminished and the heart is dilated due to artificial auricular fibrillation, the administration of digitalis results in increase in cardiac output and decrease in cardiac size. When the normal rhythm returns, the heart being of course still under the influence of digitalis, either the output increases, the size remaining unchanged (from that in the fibrillatory state), or both output and size decrease.

The observations show, as do the ones next to be reported, that digitalis has the same action in normal and in pathological hearts; it decreases cardiac size (an effect on tone). The amount of cardiac output which results from this action depends upon the initial size of the heart; it decreases in normal hearts and increases in dilated ones. In a dog, the subject of edema due to taking sodium bromide, the administration of digitalis increased cardiac output, decreased cardiac size and increased the extent of ventricular excursions.

Stewart, Harold J., and Cohn, Alfred E.: Studies on the Effect of the Action of Digitalis on the Output of Blood From the Heart. III. Part 1. The Effect on the Output in Normal Human Hearts. *J. Clin. Investigation* 11: 917, 1932.

The effect of giving digitalis to six normal individuals was studied with particular reference to its effect on cardiac output, on cardiac size and on venous pressure. The following phenomena were observed: (1) the output of blood from the heart decreased; (2) the size of the heart diminished; (3) slight decrease in cardiac rate occurred; (4) the effects were at a maximum four to twenty-four hours after giving the drug; (5) significant changes did not occur in the levels of arterial and venous pressure; (6) changes in form, sometimes slight, of the T-waves of the electrocardiogram occurred in each instance and were present as early as two and one-half hours after the drug was given; (7) as an effect of digitalis wore off (forty-eight hours to three weeks), output, size, rate and the T-waves of the electrocardiogram returned toward their initial values; (8) a correlation was not established from these data between decrease in cardiac output and change in the level of venous pressure.

Stewart, Harold J., and Cohn, Alfred E.: Studies on the Effect of the Action of Digitalis on the Output of Blood From the Heart. III. Part 2. The Effect on the Output of Hearts in Heart Failure With Congestion, in Human Beings. *J. Clin. Investigation* 11: 933, 1932.

A consequence of the action of digitalis is to decrease the volume output of blood per minute from the heart in normal human beings and to decrease its size. The volume output of blood per minute from the heart which is in failure is diminished and its size is larger than when it is in a state of compensation.

Following the administration of theocaine in patients during heart failure, cardiac output increases and cardiac size and venous pressure diminish. Giving digitalis increases the volume output of blood per minute from failing hearts and decreases the size.

Digitalis, it is thought, has similar, perhaps identical, actions both in normal and in diseased hearts; it decreases cardiac size and increases the extent of ventricular contraction. The consequence of these actions is that the volume of the cardiac output which results differs, depending on an initial difference in size of the ventricular cavities in the two situations. In the one, the normal heart, it becomes too small; in the other, the diseased heart, it develops a suitable size.

Chapman, C. W., and Morrell, C. A.: On the Biological Assay of Digitalis and Strophanthus. *J. Pharmacol. & Exper. Therap.* 46: 229, 1932.

A frog method for the biological assay of digitalis and strophanthus preparations is described in detail. The method eliminates the effect of individual variation in the frogs and variations which occur from time to time. The results of a series of assays on tinctures of digitalis and strophanthus are presented.

The official U. S. P. X. method is discussed with the method described. The wide fluctuations in the M. S. D. values for ouabain are attributed to neglect of the effect of individual differences in the sensitivity of the frogs. Seasonal, diurnal and species variations are discussed.

It is maintained that the frog method, using the technic described, combines accuracy, simplicity and economy to a greater degree than do other methods.

Anthony, Albert J., Cohn, Alfred E., and Steele, J. Murray: Studies on Cheyne-Stokes Respiration. *J. Clin. Investigation* 11: 1321, 1932.

The influence on Cheyne-Stokes respiration of breathing varied mixtures of carbon dioxide and air has been studied in periods both of short and of long duration. Increase in concentration of carbon dioxide in the air inhaled prolongs the respiratory phase and decreases the apneic phase until continuous breathing appears. Increase in the concentration of oxygen up to 80 per cent in the air inhaled prolongs the respiratory phase markedly. The duration of apnea is sometimes increased and sometimes remains constant. Inhaling oxygen in greater concentrations than that of air does not usually result in continuous breathing.

If the treatment of Cheyne-Stokes respiration has as its object the restoration to normal of the concentrations of the gases in the blood, then bringing about continuous respiration need not of itself be regarded as improvement, because continuous breathing alone does not necessarily mean that the ventilation is more nearly sufficient. For example, two patients with Cheyne-Stokes respiration were observed in whom the last stage of their disease was accompanied by an increase in cyanosis and return to continuous breathing at one and the same time. If the object of treatment is to bring about continuous respiration, then inhalation of carbon dioxide in a chamber may be attempted using the smallest concentration necessary to assure this result. To decrease the rhythmic recurrence of lack of oxygen, the effect of inhalation of oxygen in the chamber may also be utilized as is shown by the analysis of blood of patients while they are in the oxygen chamber.

Palmer, Robert Sterling: The Hypotensive Action of Potassium Sulphocyanate in Hypertension. *Am. J. M. Sc.* 8: 473, 1932.

Thirty-five well controlled patients, most of them showing the effects of continued arterial hypertension have been treated by potassium sulphocyanate. This drug when used in sufficient dosage caused a definite and marked lowering of the arterial blood pressure in 31 per cent of the patients.

Toxic effects were skin rashes, gastrointestinal symptoms and central nervous system symptoms such as acute apprehension and excitement which may be severe enough to constitute a toxic psychosis. Weakness may accompany the use of the drug but is probably not a toxic effect and does not necessarily contraindicate its use. Angina pectoris in those subject to this symptom may be increased and in some patients may be induced by use of this drug. Toxic effects were reduced to the minimal by carefully controlled dosage.

Limited observation of the use of the drug in combination with a general régime including rest and diet suggests that it may be of value, though these results may not be referred to in accurately appraising the hypotensive action. Generally speaking it may be said that the hypotensive effect is not lasting and that a second or third such effect after the drug is once discontinued is more difficult to obtain.

Prodger, Samuel H., and Ayman, David: Harmful Effects of Nitroglycerin. *Am. J. M. Sc.* 184: 480, 1932.

Nitroglycerin in therapeutic doses was administered to 110 patients under direct observation. Alarming toxic reactions were observed in four cases. In two instances the blood pressure became indeterminable and the pulse could not be palpated. Heart-block developed in one of these, and in the other the course of a cardiac infarction was thought to be unfavorably influenced. A record was made of the electrocardiographic changes

which occurred during the reactions in these two cases. In the other two cases there were, as evidence of toxicity, marked slowing of the pulse rate, great drop in blood pressure and severe constitutional symptoms.

Careful supervision of the patient is advised when the first dose of nitroglycerin is administered in order that those who have an idiosyncrasy to it may be discovered and possible dangerous reactions avoided. A small initial dose is advised. The possible harmful effects of nitroglycerin in coronary thrombosis are discussed.

Gold, Harry, and Modell, Walter: The Action of Quinidine on the Heart in the Normal Unanesthetized Dog. J. Pharmacol. & Exper. Therap. 46: 357, 1932.

The effect of intravenous injections of quinidine in therapeutic and toxic doses on the heart of normal unanesthetized dogs was studied electrocardiographically.

In both therapeutic and convulsive doses, quinidine does not produce slowing but acceleration of the sinus rate. Acceleration occurs in vagotomized dogs as well, especially in those cases in which the vagotomy does not result in an extremely rapid heart rate. In doses up to those causing convulsions, quinidine does not produce any prolongation of A-V conduction. Frequently the P-R interval is shortened simultaneously with the sinus acceleration. The drug causes prolongation of intraventricular conduction. This is sometimes in evidence with therapeutic doses but is most constant and pronounced after larger doses.

A negative T-wave becomes positive and a positive T-wave increases in amplitude. This effect of quinidine is constant in normal dogs and is a very sensitive reaction, occurring after doses as small as 2 mg. and may appear without any other changes in the electrocardiogram.

All the effects noted in the study are fleeting, coming on frequently within less than a minute after the injection and disappearing, in many cases, in less than fifteen minutes. These results are in some respects at variance with those reported in the literature. It is suggested that anesthesia and various operative procedures used in most of the previous studies on animals may be chiefly responsible for the differences.

Stieglitz, Edward J.: Therapeutic Results With Bismuth Subnitrate in Hypertensive Arterial Disease. J. Pharmacol. & Exper. Therap. 46: 343, 1932.

The present report deals with a series of 30 cases of hypertensive disease treated with bismuth subnitrate and observed over a period of several years. The basis of selection of these patients was the duration of carefully controlled observation and that no active initiating etiological factors were treated during or shortly preceding the period of observation. The therapeutic results obtained are most encouraging and gratifying.

It is believed that not only does bismuth subnitrate reduce the arterial tension in spastic hypertonia during the period over which it is administered, but, if the administration be prolonged sufficiently to permit of arteriolar rest, the arteriolar hypertonia frequently does not recur. It assists in reduction of the physiological burden of the injured structures, namely the medial musculature of the arterioles.

In the presence of extensive arteriosclerosis or active etiological sources of arteriolar irritation, bismuth subnitrate is inadequate, as would be any other mild vasodilator. In angina pectoris associated with hypertensive disease, bismuth subnitrate appears to reduce the frequency and severity of anginal attacks.

Porter, Elsie: The Therapeutic Use of Drugs of the Digitalis Group. Quarterly J. M. 2: 33, 1933.

A massive calculated dose of the tincture of digitalis at the rate of 0.125 c.c. per lb. of body weight of the patient, when administered by mouth in a single draught, is

the method of choice in treating cases of auricular fibrillation, because a perfectly good result can be obtained with certainty in six to eight hours.

In cases of vomiting from congestive failure an equally good result may be obtained by giving a similar massive dose per rectum, calculated at the rate of 0.1 c.c. per lb. of body weight.

In very urgent cases, where a still more rapid action is required, a similar result may be obtained within thirty minutes by the administration of a single intravenous dose of 1/33 gr. of strophanthin. The site of action in all three routes is similar, i. e., that they all act via the vagus, as shown by "vagal release" with atropin.

Cases of auricular fibrillation should be given the advantage of being treated by one or other of the methods described, in order that their discomfort may be relieved in a day, instead of having it prolonged to a week by the use of older methods.

Hansen, Olga S., and Maly, Henry W.: The Effects of Thoracoplasty on the Heart. *Am. Rev. Tuberc.* 27: 200, 1933.

In an attempt to determine the effects of thoracoplasty on the heart as evidenced by the electrocardiogram, 57 cases have been studied by means of electrocardiograms and x-ray films, before and after the collapse. Thirty cases of uncomplicated pulmonary tuberculosis have been taken for controls. It has been shown that the intrathoracic pathological involvement incident to thoracoplasty almost invariably displaces the heart more or less to one side or the other but most frequently toward the unaffected side. The electrocardiograms also show a high incidence of postoperative change, but these changes are neither consistent nor predictable, being in agreement with the x-ray findings in only a third of the cases. It would seem impossible to predict the probable electrocardiographic change from a study of the x-ray pictures or, conversely, to guess the type of x-ray findings from looking at the electrocardiograms. It is probable that the electrical axis may be influenced by rotation of the heart on its longitudinal axis by fibrotic tissue affecting at times the base, and at times the apex anteriorly or posteriorly. It is probable that other factors such as bed rest, toxemia and weight changes may affect the form of the electrocardiogram, since the control patients who had no gross mechanical changes were also variable in their complexes.

There has been no evidence of disturbance in conduction or of myocardial damage in the electrocardiograms. Autopsy has shown no abnormality in heart weight nor more evidence of myocardial degeneration than is found in other patients dying of tuberculosis. Some of the changes in QRS amplitude probably represent changes in muscle tone associated with reduction of toxemia and increase in exercise and would appear regardless of the mechanics of collapse. The changes found in the electrocardiogram are probably due to extrinsic factors and bear no relationship to the condition of the heart muscle.

Camp, Paul D., and White, Paul D.: Pericardial Effusion: A Clinical Study. *Am. J. M. Sc.* 184: 782, 1932.

The authors have studied the clinical and pathological data on 126 cases containing over 100 c.c. of pericardial fluid found at postmortem examination over a period of ten years occurring among 95,542 cases admitted to the hospital and among 1,729 necropsies. They conclude that without the presence of an acute fibrous pericarditis, the diagnosis of pericardial fluid is likely to be missed unless the effusion amounts to over 500 c.c. Of the 126 cases, a correct clinical diagnosis of pericardial effusion was made only 6 times.

To establish a clinical diagnosis of pericardial effusion, all signs and symptoms must be carefully looked for and analyzed and roentgen ray studies employed in all cases except a very few, where the effusion is so large and rapid in its development that the clinical diagnosis is easily made at once.

Gouley, B. A., Bellet, Samuel, and McMillan, Thomas M.: Tuberculosis of the Myocardium. *Arch. Int. Med.* 51: 244, 1933.

Six cases of tuberculous of the myocardium are reported. Four of the patients were males and two were females. Four were negroes and two were white people. The ages of the patients were 16, 16, 26, 46, 51 and 17 years. These cases represent the different types of tuberculous myocarditis that have hitherto been reported. A simple classification is suggested, based on the mode of dissemination and the type of lesion; (a) myocardial tuberculosis, secondary to mediastinal glandular and pericardial tuberculosis and (b) as part of systemic miliary tuberculosis.

Involvement of the coronary arteries in one case in an unusual degree and in other cases to slight degree is reported, and the various types of tuberculous arteritis are described: (a) diffuse tuberculous arteritis, involving all the vessel coats; (b) intimal tubercle without involvement of other vessel coats as a result of blood borne infection; and (c) a type of arterial involvement by tuberculosis (contact arteritis) previously not described in the heart, affecting not only the small but also the large coronary arteries and leading to narrowing of their lumen and even to complete occlusion.

The occasional similarity of rheumatic and tuberculous myocarditis is noted, and a differential diagnosis is outlined. The probability of ectopic rhythm resulting from the tuberculous infiltration of the right auricle is discussed.

Horton, Bayard T., and Brown, George E.: Thromboangiitis Obliterans Among Women. *Arch. Int. Med.* 50: 884, 1932.

Although approximately 700 cases of thromboangiitis obliterans have been observed among men at the Mayo Clinic, the present report of 10 cases is the first series among women to be put on record. The diagnosis in three of these cases was proved by a study of the pathological changes in the occluded arteries and veins. The authors are of the opinion that this disease has a higher incidence among women than is brought out by this study. The failure to recognize the disease is due probably to the facts that it is relatively mild among women and that the diagnosis is overlooked. Three of the patients in the series were of Jewish extraction; their disease was more severe than in the 7 gentiles. A similar clinical impression was gained in the series of men; the disease of the Jewish patients seemed more serious and intense than that in the other races.

Four patients were treated by bilateral lumbar sympathetic ganglionectomy; one of these also had bilateral cervicothoracic sympathetic ganglionectomy. One patient had an amputation of the right leg and the other patients were treated medically. The treatment, for the most part, has proved satisfactory. The disease among women apparently runs a similar but definitely milder course than among men.

Stehle, R. L.: A Method for Studying Variations in Coronary Inflow During a Series of Cardiac Cycles, or for Determining Inflow Rates Generally. *J. Pharmacol. & Exper. Therap.* 46: 471, 1932.

The method is described for use as outlined in the succeeding paper. It is a modification of the Langendorff method.

Stehle, R. L., and Melville, K. I.: The Influence of the Heart Beat Upon the Flow of Blood Into the Coronary Arteries. *J. Pharmacol. & Exper. Therap.* 46: 477, 1932.

The method of studying coronary inflow described in the preceding paper has been applied to the rabbit's heart. The results show that the inflow begins late in diastole and continues into systole. It is not restricted to diastole or to systole. In contradistinction to observations by Hochrein, these experiments indicate that the maximum flow is not restricted to an instant but lasts through a definite period. The authors

believe that their results are in agreement to a considerable extent, with those obtained by Aurep. The authors also compare their results with the data published by Roessler and Pasenal.

Katz, Louis N., Hamburger, Walter W., and Rubinfeld, Samuel H.: Observations on the Effects of Oxygen Therapy. II. Changes in the Circulation and Respiration. Am. J. M. Sc. 184: 810, 1932.

A comparison of the effects of oxygen therapy on the circulation and respiration of a group of cardiac and noncardiac patients was used as a check on the clinical impressions and to determine whether these changes preceded, accompanied or followed the clinical improvement. A modified direct venous pressure method is described and also a simple clinical method of determining minute volume of respiration.

Oxygen therapy tended to decrease the vital capacity slightly; it caused no significant changes in arterial and venous pressure. An increase in the amplitude of QRS and an increase in the size and duration of the T-wave were found in the majority of cases during exposure to an oxygen-rich atmosphere.

Oxygen therapy was found to result in (1) a slowing of the heart by causing a sinus bradycardia, (2) a decrease in minute volume of respiration, and (3) an increase in the length of time the breath could be held. These changes tend to occur as readily in the noncardiac case as in the cardiac and in the latter in spite of advancing failure. These changes are primarily the result of the oxygen-rich environment and seemed in part, at least, independent of relief of arterial anoxemia. These changes in heart rate, in breath holding ability and in minute volume of respiration are in themselves beneficial and may be ways, aside from relief of arterial anoxemia, by which oxygen therapy may act beneficially in cases of heart failure. No slowing of ventricular rate occurred in cases with auricular fibrillation, and less beneficial effects may be expected from oxygen therapy in such cases. No direct diuretic effect was observed as a result of oxygen, either in the edematous or nonedematous patients.

Cohn, David J., Katz, Louis N., Soskin, Samuel, and Hamburger, Walter W.: Observations on the Effects of Oxygen Therapy. III. Blood Chemical Changes. Am. J. M. Sc. 184: 818, 1932.

The function of oxygen therapy is not to attack the underlying causes of the disease but to give the patient the benefit of as high a blood oxygen saturation as possible. It is conceivable that some of the benefits of oxygen therapy may be produced in other ways besides the improvement of arterial anoxemia. However, the major benefit of oxygen therapy is the increase in oxygen saturation of the arterial blood, thus relieving the arterial anoxemia and its effects.

Asher, A. Graham: Graphic Registration of Heart Sounds by the Argon Glow Tube. Arch. Int. Med. 50: 913, 1932.

A new method for photographing heart sounds has been described, the Argon Glow tube being used. Once the necessary apparatus was set up, the method was found to be simple. It could detect the ordinary and obscure heart sounds. Illustrations of some of its uses in clinical cases are described, and suggestions for its further applications are offered.

Hudson, Charles L., Moritz, Alan R., and Wearn, Joseph T.: The Extracardiac Anastomoses of the Coronary Arteries. J. Exper. Med. 56: 919, 1932.

In a series of experiments planned for the purpose of injecting the vessels in the heart valves, a colloidal suspension of carbon particles was injected into the coronary arteries of human hearts which had been excised at autopsy. When one came to

study the injected specimens, it was soon observed not only that the vessels in the heart were filled with the carbon particles but also that the arteries in attached flaps of the parietal pericardium contained the injection mass. Further observation showed that an extensive network of vessels in the adventitia of the aorta and pulmonary artery was also injected. These observations led to a more thorough study of the extracardiac anastomoses of the coronary arteries.

It was found that widespread anastomoses of the auricular branches and the coronary branches to the pericardial fat with the pericardiophrenic branches of the internal mammary arteries and the anterior mediastinal, pericardial, bronchial, superior and inferior phrenic, intercostal and esophageal branches of the aorta were present. The most extensive anastomoses between the cardiac and extracardiac vessels were around the ostia of the pulmonary veins. It was possible not only to demonstrate the passage of injection mass from the coronary arteries into the vessels of surrounding structures, but also to show vessels in the heart injected through the thoracic branches of the aorta.

This rich potential extracardiac coronary collateral circulation is probably of significance in compensating for sclerosis of the large trunks of the coronary arteries.

Moritz, Alan R., Hudson, Charles L., and Orgain, Edward S.: Augmentation of the Extracardiac Anastomoses of the Coronary Arteries Through Pericardial Adhesions. *J. Exper. Med.* 56: 927, 1932.

The examination of four hearts with partial or complete obliteration of the pericardial sac by fibrous adhesions, after injection of the coronary arteries with a colloidal suspension of lamp black showed that the extracardiac anastomoses of the coronary arteries were increased owing to the presence of adhesions. In all four instances a particularly high injection of the parietal pericardium was obtained and microscopic examination of the adhesions showed them to contain injected vessels, extending from epicardium to parietal pericardium. A microscopical study of cleared blocks (3 mm. in thickness) of myocardium and attached pericardial adhesions, showed the arborization and anastomosis of branches of the arteries of the parietal pericardium with those of the heart. This vascularization was not limited to the usual areas of subepicardial fat but was seen in regions not ordinarily containing arterial branches. In no one of the four cases were the coronary arteries significantly diseased.

In one of the four cases, the normal sites of anastomoses between the cardiac and extracardiac vessels were destroyed by cutting away the great vessels entering and leaving the heart, as well as the peri- and intervacular reflections of parietal pericardium. Injection mass was found, however, in the arteries of the parietal pericardium and the diaphragm, showing that it has passed directly through the adhesions from coronary to extracardiac vessels.

If the extracardiac anastomoses of the coronary arteries constitute a significant reserve for cardiac circulation, it would appear that this reserve would be augmented by the presence of pericardial adhesions. Direct communication between branches of the coronary arteries and the pericardial branches of the internal mammary arteries with free anastomosis with the anterior branches of the thoracic aorta is established over areas corresponding to the extent of the adhesions. Work is in progress to study the functional significance of such an experimentally induced collateral circulation in experimental coronary occlusion.

Victor, Joseph: The Effects of Sugar and Electrolyte Solutions on the Metabolism and Irritability of Heart Muscle. *Am. J. Phys.* 103: 620, 1933.

Isotonic solutions of potassium chloride and sucrose depress the oxygen consumption of irritable and nonirritable cardiac muscle. This is associated with a decrease

in muscle tone and loss of irritability. Isotonic calcium chloride increases both the tone and the metabolic rate of irritable and nonirritable heart muscle but renders the irritable muscle nonirritable. The antagonistic action of potassium chloride and sucrose and of calcium chloride on the metabolic rate and tone of heart muscle is found to be opposite that of irritable skeletal muscle. Furthermore, the action of these substances is independent of the previous state of irritability of heart muscle but varies with the previous state of irritability of skeletal muscle. If spontaneous sugar or potassium nonirritability in cardiac muscle is due to the same causes as obtain in skeletal muscle, the similarity of the action of sucrose and potassium solutions may be due to the washing away of calcium by the sucrose solution and thus increase the potassium chloride ratio at the surface membranes of the muscle fibers. Furthermore, if the differences observed are due to membrane equilibria, it might be suggested that heart muscle differed from skeletal muscle in having its membranes reversed and that a similar reversal of equilibrium was responsible for the phenomenon of nonirritability in skeletal muscle. Much more study, however, is required before theorizing in these matters will be profitable.

The metabolic rate of nonirritable cardiac muscle first decreases, then after several hours increases, and finally returns to normal after immersion in an isotonic solution of glucose. Ringer's solution slightly depresses the oxygen consumption of spontaneously nonirritable cardiac muscle but has no effect on the metabolic rate of irritable heart muscle.

Hydrochloric acid in concentrations above 0.01 M in isotonic sodium chloride decreases the oxygen consumption of spontaneously nonirritable heart muscle. Methylene blue increases the oxygen consumption of irritable and nonirritable heart muscle.

McGinty, Daniel A., and Miller, A. T., Jr.: Studies on the Coronary Circulation.

II. The Absorption of Lactic Acid and Glucose and the Gaseous Exchange of Heart Muscle. *Am. J. Phys.* 103: 712, 1933.

With the accumulation of data showing that lactic acid is absorbed by the heart of the dog in amounts corresponding to the quantity of material generally accepted as being oxidized as carbohydrate, it was found necessary to reopen the study of oxidations in cardiac muscle and to investigate the manner of disposal of absorbed lactic acid. Two methods were employed: first, perfusion of an isolated beating heart by arterial blood from a donor dog, and second, perfusion of the beating heart in situ. In either method, simultaneous samples of ingoing arterial blood and outgoing coronary venous blood were analyzed for lactic acid, glucose and oxygen and carbon dioxide content. Coronary volume flow of blood was recorded. Perfusions were carried out for thirty to ninety minute periods, blood samples being taken at five to nine minute intervals.

In 5 experiments on perfusion of the isolated heart with a total of 53 pairs of blood samples, the average lactic acid absorption was 1.5 mg., glucose absorption 0.2 mg. and oxygen absorption 3.5 c.c. per gram of heart muscle per hour. Blood flow amounted to 42 to 55 c.c. per gram per hour. In 7 experiments with the heart intact within the open thorax in 65 samples, average lactic acid absorption amounted to 3.1 mg., glucose 0.39 mg. and oxygen intake 5.1 c.c. per gram heart per hours. Mean coronary flow was 49 c.c. In the first group of observations, the respiratory quotient was below 0.70 in three and above 0.70 in two. In the latter group, a respiratory quotient below 0.70 occurred in but 1 experiment.

The results indicate that glucose is not absorbed at all or is absorbed in but small amounts while lactic acid is removed from the coronary arterial blood in quantities, which suggest its utilization as the carbohydrate fuel of the heart. The results of other workers who interpreted the loss of glucose from perfusion fluids as indicating

its absorption by the heart are criticized on the basis of failure to exclude decomposition of glucose as a result of bacterial action. This has been shown to be an important source of error in perfusion procedures. Furthermore, those who worked with blood as a nutrient fluid have failed to consider glycolysis in blood, which takes place with significant rapidity.

The status of the glycogen stores of the heart was not investigated; although a review of literature indicates that under the experimental conditions which prevailed, the glycogen content of the heart was neither increased nor drawn upon for carbohydrate oxidation. Significance of the respiratory quotient as an index to the fuel of the heart is criticized. It is believed that this quotient is of questionable value in determining the nature of oxidations in isolated organ perfusion. Under more normal experimental conditions, it may assume greater significance.

McGrea, F. D., and Wiggers, Carl J.: Rhythmic Arterial Expansion as a Factor in the Control of Heart Rate. *Am. J. Phys.* 103: 417, 1933.

In a series of experiments, the heart rate changes which occur reflexly or directly when pulse pressure and mean pressure were varied as independently as possible were studied. Aortic pressures were optically recorded and systolic, diastolic and pulse pressures calculated from records by use of a calibration scale. Mean pressure values were arrived at accurately by measuring the area beneath the pressure curve and dividing by horizontal distance.

The effects produced by various procedures, such as compressing the vena cava and aorta, served no useful purpose in settling the problem, as pulse pressure and mean pressure changed in the same direction. They were useful in determining that under such conditions a mean pressure variation of 4 to 5 mm. is the minimal which causes any certain change in heart rate.

After saline infusion, which increases the pulse pressure, a cardiac slowing was obtained in a sufficient number of experiments in which no change or a decrease in mean pressure took place. These results were suggestive of a separate effect of pulse pressure but in view of some apparently negative effects could not be regarded as conclusive.

Through the expedient of producing experimental aortic insufficiency it was found possible to increase pulse pressure and simultaneously decrease mean pressure; further, by compressing the thoracic aorta to a suitable extent, mean pressure was often restored approximately or exactly to normal, while pulse pressures increased still more. It was found that frequently the heart rate slowed despite a sharp decline of mean pressure and with one exception was always retarded when mean pressure was restored to normal levels by compression. While the control of heart rate by pulse pressure changes was demonstrated, the results on the "whole animal" permitted no conclusions as to whether the effects were induced by direct or reflex action.

A second set of experiments was performed in order to determine whether changes of pulse pressures in a cephalic end of a perfused carotid artery can reflexly cause heart rate changes when mean pressure either remains unaltered or deviates in a reverse direction. To do this, pressure pulses were recorded simultaneously from the perfused carotid and the animal's own artery by means of optical manometers.

Perfusion of the cephalic end of a carotid artery with a constant pressure in the perfusion system was found not to produce a constant pressure within the artery itself owing to effects of collateral circulations. The magnitude of the pulsation varied inversely as the perfusion pressure used, being larger when pressures were low and small when they were high. Such dynamic effects complicate the interpretation of results of previous investigations.

A sudden change in pressure appeared more potent in producing temporary alterations in heart rate than permanent levels of pressure established. Alteration of the

perfusion pressures and rhythmical variations in such a way that pulse pressure increased in the perfused vessel while mean pressure remained unaltered or was even reduced were attended by cardiac slowing unless the reduction was too extreme. This demonstrates that pulse pressure variation dominates the production of reflex cardiac changes.

The conclusion is reached that Marey's law requires amendment; changes in mean pressure levels indeed control heart rate changes reflexly but only so long as pulse pressures do not change too much in an opposite direction. When this is the case, the effects of pulse pressure changes dominate the reactions.

Korns, Horace M., and Guinand, P. H.: Inequality of Blood Pressure in the Brachial Arteries, With Especial Reference to Disease of the Arch of the Aorta. *J. Clin. Investigation* 12: 143, 1933.

The data obtained by bilateral brachial pressure measurements in 1000 normal subjects are presented and analyzed. What has been arbitrarily designated as a significant sphygmie inequality occurred 439 times in 378 persons; nearly three-fourths of the higher pressures were dextrolateral. Significant inequalities in pulse pressures appeared in 274 persons, 67 of whom failed to show differences of 10 mm. or more between the two systolic or diastolic levels; nearly three-fourths of the higher pulse pressures were dextrolateral. These pressures were measured simultaneously in both arms, but for all practical purposes consecutive measurement gives equally satisfactory results.

The fact that inequalities in the blood pressures and volume of the pulse in the right and left brachial arteries may or may not indicate disease of the aorta or its branches is illustrated by the presentation of case reports.

Sphygmie inequality without organic disease is probably always transitory, and it is reasonably certain that all normal persons manifest it at one time or another. The inequality may involve only the systolic pressures, or only the diastolic, or both; and if both levels are disparate, the inequality may be concordant (both right higher than both left, or vice versa) or discordant (right systolic higher than left and left diastolic higher than the right or vice versa). In some persons the higher pressure is irregularly heterolateral; in others it appears to be always homolateral. There is no evidence that right or left handedness plays any rôle. The physiology of transitory disparities in brachial pressures is not understood. Sphygmie inequality in the brachial or carotid arteries cannot be regarded as a sign of disease of the aorta or its branches unless it can be shown to be permanent.

Starr, Isaac, Jr., Collins, Leon H., Jr., and Wood, Francis Clark: Studies of the Basal Work and Output of the Heart in Clinical Conditions. *J. Clin. Investigation* 12: 13, 1933.

Using a method devised by Starr and Gamble, involving a modification of the Henderson and Haggard ethyl iodide method for the estimation of cardiac output, the authors have made duplicate determinations of cardiac output and metabolism, repeated estimations of blood pressure and pulse rate and orthodiagrams in 50 individuals. These estimations were performed on fasting subjects lying at rest after a prolonged rest period. Those tested included apparently normal persons, persons who had recovered from congestive failure and patients with some circulatory abnormality but not immediately threatened with failure, namely, thyrotoxicosis, hypertension anemia, angina pectoris, compensated valvular disease, and functional heart disease. The authors present an extensive discussion of the details of the method together with a résumé of the technical difficulties encountered in carrying on such a study, particularly the estimation of the cardiac output and the establishment of basal conditions.

When the basal work of the left heart of these subjects was plotted against the volume of the heart or the area of the cardiac silhouette, the points representing cases

not threatened with failure were found to be arranged about a straight line. On the other hand, the points representing cases threatened with failure are outside the limits of the normal cases.

The results obtained are regarded as evidence that Starling's "Law of the Heart" holds for the basal cardiac work in diverse clinical conditions as well as for the heart lung preparation. Paraphrasing his words it may be said, "Within physiological limits the larger the size of the heart, the greater is the energy of its contraction." And as a corollary, when the work of any heart is not commensurate with its size, that heart is threatened with failure.

On the basis of a diverse group of cases believed to have normal myocardia, the authors have made a preliminary estimate of the normal relationship between heart work and size. Charts and equations are submitted by which the question of the normality of any case may be decided.

The relationship between heart size and heart work per beat was equally striking in 17 cases of hypertension. Those with hearts of normal size, by reducing cardiac output, maintained their hypertension without greater expenditure of cardiac work than normal persons. The patients with large hearts were performing increased work. Considering increased cardiac work as cause of hypertrophy in the latter group, its absence will explain the absence of hypertrophy in the former.

The cardiac output was directly related to the metabolism in the cases not threatened with failure. The arteriovenous oxygen difference was much smaller in these patients than in those who had been decompensated. The cardiac output was related to the size of the heart but, as a rule, not so closely as was the cardiac work. There was a surprising lack of correlation between cardiac output and body surface area in cases of hypertension; the remainder of the control cases showed correlation above the level of significance.

Although the errors in estimating basal cardiac output or work are undoubtedly large, the differences found in clinical conditions are so much larger that the results, properly interpreted, have clinical significance.

Levinson, Samuel A., and Learner, Aaron: Blood Cysts on the Heart Valves of New-born Infants. Arch. Path. 14: 810, 1932.

In 16 consecutive postmortem examinations of infants, 12 showed blood cysts on the valves. These blood filled cysts appeared as small circumscribed, dark red, elevated nodules found on the mitral and tricuspid valve leaflets, infrequently on the pulmonic leaflets and rarely on the aortic. They varied in number from 2 or 3 to 10 or 15, though as many as 30 have been reported. The nodules project above the auriculoventricular leaflets near the free margin between the edge and the line of contact on closure. On histological examination, the nodules as seen in cross-section appear as monolocular or bilocular or even multilocular spaces filled with red blood cells. The spaces are lined by a single layer of endothelial cells, in appearance similar to the surface endothelium of the valve leaflets. A discussion is given of the possible manner of origin of these nodules.

Evans, William: Congenital Stenosis (Coarctation), Atresia, and Interruption of the Aortic Arch. Quarterly J. Med. 2: 1, 1933.

Instead of the usual classification proposed by Bonnett dividing cases of coarctation of the aorta into the infantile and adult types, the author proposes to introduce a classification whereby the cases are allotted to different groups according to the nature of the anatomical deformity present and the arrangement of the associated or compensatory lesions. In this way it would be possible to define six separate types of congenital stenosis and atresia of the aortic arch. In order to allocate a case to its particular group, it is necessary to consider the following data: (1) the site, nature and extent

of the constriction; (2) condition of the aorta proximal to the site of stenosis; (3) patency or otherwise of the ductus arteriosus; (4) relationship between the systemic and pulmonary circulation. The adoption of the proposed classification will also facilitate the interpretation of certain clinical findings presented by these cases and more especially will help to explain such appearances as are found on radiological examination of the heart and great vessels. It will also help to determine the nature of the changes that are the direct result of a modified circulation initiated by the presence of this congenital deformity.

The six types are enumerated as follows: Type I, congenital stenosis of the aortic arch with patent ductus arteriosus and hypoplasia of the proximal portion of the aorta. Type II, congenital stenosis of the aortic arch with a ductus arteriosus closed and hypertrophy of the proximal portion of the aorta. Type III, congenital atresia of the distal portion of the aortic arch with ductus arteriosus closed and hypertrophy of the proximal portion of the aorta. Type IV, interruption of the aortic arch in its distal portion with a ductus arteriosus widely patent and hypoplasia of the proximal portion of the aorta. Type V, congenital atresia of the proximal portion of the aortic arch with a ductus arteriosus patent. Type VI, congenital absence of the ascending aorta with patent ductus arteriosus. Features that characterize each of the six types are outlined, and a short description of the cases is appended in each group.

In a study made on 28 cases of congenital stenosis, atresia or interruption of the aortic arch, 26 of which had been examined at autopsy, it was found possible to separate the cases into definite types according to the anatomical features present.

Patients living beyond early infancy were found in Types I, II and III only; few in Type I with the ductus patent and more in Types II and III with the ductus closed. Other developmental abnormalities that may accompany this congenital deformity of the aortic arch are enumerated.

No one symptom or collection of symptoms could be claimed to indicate with certainty the diagnosis of congenital stenosis of the aortic arch. In infants the exact nature of the lesion can only rarely be established. A tentative clinical diagnosis of congenital heart disease is usually made. It is also rare for any subjective symptom occurring in an adult suffering from this condition to direct attention to the initial lesion which has caused the illness. The author believes that symptoms presented by one of the patients may prove peculiar to, or either pathognomic of, the condition. This patient complained of numbness and weakness in both legs whenever he assumed the upright posture after reclining for some little time in the horizontal position. As he changed from the latter to the former posture, he experienced a sensation of "blood rushing back to the legs." He states that the sensation was comparable to the one he experienced when the pressure within the pneumatic bag of the sphygmomanometer placed around the thigh was released. These symptoms disappeared on walking a short distance and were never precipitated by the act of continued walking. It is seldom very safe to rely upon physical signs obtained from examination of the heart as indicating the diagnosis of this congenital lesion. The deformity is a vascular one, but owing to its proximity to the heart, the latter does undergo certain changes which have been described and which give rise to certain physical signs. A short note has been added on the prognosis and manner of death in patients presenting this congenital anomaly.

Graef, Irving, Parent, Solomon, Zitron, William, and Wyckoff, John: Studies in Rheumatic Fever. I. The Natural Course of Acute Manifestations of Rheumatic Fever Uninfluenced by "Specific" Therapy. *Am. J. M. Sc.* 185: 197, 1933.

This study is based on a series of 162 patients suffering from acute rheumatic fever admitted to the hospital during two years. The observations made on 105 of these patients receiving no form of therapy which might be considered specific and no anti-pyretic drug formed the basis of the report. Only 47 of the 105 patients fulfilled the

criteria set up for purposes of the study. It is concluded that in adolescence and adult life the acute manifestations of rheumatic fever tend to subside spontaneously. These manifestations vary in number, degree and duration, and are discussed by the authors.

If changes in the number, degree and duration of manifestations are used as criteria for determining the effect of therapeutic agents, such changes must be compared either with a standard control group of rheumatic fever patients of known age, sex, racial and proper geographical distribution, of sufficient size to meet statistical requirements; or controlled cases must be studied simultaneously with cases receiving "specific" therapy, in sufficient number so that it may be determined whether or not the effects associated with treatment are not simply variations attendant on the natural course of the disease.

Clawson, B. J., Wetherby, Macnider, Hilbert, E. H., and Hilleboe, H. E.: *Streptococcic Agglutination in Chronic Arthritis and Acute Rheumatic Fever*. *Am. J. M. Sc.* 184: 758, 1932.

Streptococci agglutination titers were determined in chronic arthritic and acute rheumatic fever patients for two strains of streptococci. The first strain was isolated from a case of acute rheumatic fever and the second from a case of chronic arthritis. Comparing the agglutination titers of the above conditions with those of normal persons and of patients with scarlet fever and glomerulonephritis, with the rheumatic strain the agglutination titers of acute rheumatic patients were higher than normal, while those of the chronic arthritic patients were not. With the chronic arthritic strain, the titers were higher than normal in both chronic arthritis and acute rheumatic fever, but higher in the latter. With both strains the titers were decidedly higher than normal in both scarlet fever and glomerulonephritis. In all tests including the normal serums, the chronic arthritic strain was agglutinated in higher dilutions than the acute rheumatic strain. The chronic arthritic strain appeared to be more sensitive to agglutination.

These findings suggest that both chronic arthritis and acute rheumatic fever are streptococcal infections. The view that chronic arthritis is due to a specific strain is not supported, since the chronic arthritic strain was agglutinated in higher dilutions with serums from acute rheumatic fever patients than with the serums of patients with chronic arthritis. The lack of strain specificity is also shown by the fact that both the rheumatic and the arthritic strains were agglutinated in higher dilutions with serums from scarlet fever and glomerulonephritis than with the serums from acute rheumatic fever or chronic arthritis.

Collis, W. R. F., Sheldon, Wilfrid, and Hill, N. Gray: *Cutaneous Reactions in Acute Rheumatism*. *Quarterly J. Med.* 1: 511, 1932.

The present investigation was undertaken with the view to elaborating and confirming previous observations with hemolytic streptococcal endotoxin on a larger series of cases and at the same time ascertaining whether any analogy existed between the cutaneous reactions to this hemolytic streptococcal extract and to similar products of non-hemolytic streptococci and other pathogenic bacteria.

Skin reactions of 303 rheumatic children have been tested, while 256 nonrheumatic children have been similarly examined to serve as controls. The rheumatic series consisted of children who were at the time suffering from or had previously suffered from polyarthritis, carditis or chorea.

The results obtained indicate that rheumatic children are more sensitive to streptococcal extract than are nonrheumatic children, and that of the rheumatic children those with chorea are the most sensitive. Children with active rheumatism, and for a period of six months after the acute attack, show a high percentage of strongly positive reactions (80 per cent). After six months, this reactivity diminishes. Children with ful-

minating carditis lose their skin reactivity during the severe phase of their illness, though they tend to regain it later. Patients with chronic cardiac failure also tend to give much reduced reactions. Age seems to be an important factor in determining the probability of positive reactions up to the age of puberty. The curve is seen to rise in an almost straight line up to twelve to fourteen years, after which it ceases to rise.

Skin reactions to hemolytic streptococcal extracts appear to bear no relation to skin reactions with hemolytic streptococcal exotoxin (Dick toxin).

A comparative study of the skin reactions of extracts of hemolytic, green and non-methemoglobin forming streptococci appears to indicate that these extracts do not contain a common active principle but that each extract gives a specific skin reaction. Rheumatic children, when tested to extracts of two viridans streptococci and one gamma streptococcus, only showed a higher percentage of strongly positive reactions to one of the viridans extracts than did the controls.

Skin reactions of rheumatic children to tuberculin, Schick toxin and extracts from pneumococci, staphylococci, diphtheroid bacilli and Pfeiffer's bacillus do not show a higher sensitivity than do nonrheumatic children and thereby differ from the skin reactions produced by hemolytic streptococcal extract.

Book Reviews

L'ANGINE DE POITRINE: FORMES CLINIQUES, TRAITEMENT MÉDICAL ET CHIRURGICAL.
By Camille Lian with the collaboration of A. Blondel, G. Huret, M. Marchal and H. Welti, 429 pages, Paris, Masson et Cie, 1932.

The authors divide angor into five types: (1) cardio-arterial, (2) cardiaque, (3) réflex, (4) toxique, and (5) neurotique. The cardio-arterial type which includes four-fifths of all cases has three subdivisions: (a) the common form of cardio-arterial angor, (b) acute febrile coronary angor, and (c) abdominal angor. The cardio-arterial angor is regarded as due to overburdening of the left ventricle whether from vasomotor disturbance, coronary stenosis, aortitis or "hypertrophic dilatation." The so-called cardiaque angor is caused by such conditions as rheumatic valvular disease or paroxysmal tachycardia. Reflex angor is due to gastrointestinal disturbances, cholelithiasis or left-sided thoracobrachial neuralgia. It occurs in the absence of heart disease. Toxic angor is due to intoxication from hypothyroidism, gout, or tobacco, although the last is seldom important. The neurotic type is an hysterical pseudo-anginal phenomenon.

Most of the book is devoted to clinical descriptions of the various types of angor. A few pages are given to the pathological anatomy of acute febrile coronary angor. The electrocardiographic findings of the common form and the acute febrile coronary forms of cardioarterial angor are discussed.

Considerable space has been devoted to treatment. The three "treatments of choice" in the so-called cardio-arterial angor are: (1) intravenous injection of iodides, (2) subcutaneous injection of carbon dioxide, and (3) irradiation. Most of the other methods of treatment, including a variety of drugs, hygienic, physiotherapeutic and surgical procedures are mentioned. Removal of the stellate ganglion is discussed in some detail, although only two of the authors' cases were subjected to this procedure.

The references, which are mainly to the French literature, include 37 papers by the senior author. The book will therefore be of interest to all who wish to acquaint themselves with contemporary French thought on the subject. The reader, however, will not find an authoritative discussion of the recent work on the relationships between disturbances in blood supply of the myocardium and anginal types of pain. Recognition of the importance of this work should have compelled a new classification and a rewriting of the sections dealing with the causes of anginal types of pain. These defects seriously limit the usefulness of the book.

—C. C. W.

THE HEART RATE. By Ernest P. Boas and Ernst F. Goldschmidt. 1932, 166 pages, Springfield, Ill., and Baltimore, Md., C. C. Thomas.

Boas and Goldschmidt present in a small volume the results of an extensive study of the heart rate in 356 individuals, 103 of them being normal controls. They employed the Boas cardi tachometer, an electrical instrument which amplifies and records the action current of each heart beat. The machine is attached to the subject of the experiment by means of long leads so that it is possible to observe all sorts of bodily activity during the day and what is just as important, the phenomena of sleep. The authors have investigated the many factors which influence heart rate, especially the results of emotion, exercise, hot and cold food and the varying conditions of sleep. Particularly instructive are their observations on the morning toilet which in several normal controls raised the pulse rate above 110. The many excellent tracings in the book record the effects of those homely and intimate events of daily life which have escaped scientific

study in normal people, although it is well known that they may precipitate acute cardiac failure in patients with heart disease.

Perhaps the most illuminating data for clinicians are the averages obtained on the 51 normal men and 52 normal women, most of whom were young:

	AV. RATE FOR WAKING HOURS	BASAL AWAKE	AV. RATE FOR SLEEPING HOURS	MINIMUM ASLEEP
Men	77.8	61.4	59.4	52.8
Women	83.9	69.9	65.3	57.7

The authors emphasize the importance of obtaining true basal conditions for comparative purposes, and they point out the clinical value of measurements made during sleep, especially in the differential diagnosis of neurocirculatory asthenia. Their detailed studies of the heart rate in cardiac patients are of great interest. The curves of rates during the different stages of operations should be scrutinized by internists as well as surgeons.

This little book is one that should not be neglected by physicians or physiologists. The subject matter is well presented and the authors keep a good sense of proportion. They do not lose sight of the fact that the heart rate is only one of many factors in the circulation.

—E. F. Du B.

THE FAILING HEART OF MIDDLE LIFE. By A. S. Hyman and A. E. Parsonnet. The F. A. Davis Co., Philadelphia, 1932.

This book, with greater accuracy, might have been entitled "coronary arterial disease," inasmuch as five-sixths of the text is devoted to this subject. Of the heart that fails in middle life as a result of rheumatic, syphilitic, or hypertensive disease, nothing is said.

It is not made clear for whom the book was written. There are intimations that it is intended for the practitioner, but if so, it is scarcely justifiable to devote almost a fourth of its pages to a detailed discussion of electrocardiograms, and another fourth to an exhaustive presentation of the various theories relating to angina pectoris. The general approach of the authors is revealed in their statement: "Indeed, the very approach to the simplest discussion of the anginal syndrome must carry one over pathways of the most intangible and complicated sort, proceeding through a labyrinthine maze of neurologic, myogenic, and teleologic routes." In view of this attitude, with which the present reviewer is not in sympathy, it is not surprising that the chapter on angina is the longest and most involved in the volume. It is regrettable that their learned discussion of this type of heart failure should leave the careful reader with his impressions blurred and confused rather than clarified, for there are many features of angina that may be described clearly and dogmatically, even though some are still puzzling.

The book as a whole leaves the impression of being too long; with the exception of the last chapter, it would have been improved by considerable reduction. In their apparent desire to leave no topic untouched, the authors have extended their discussions and descriptions unduly, and in many instances have introduced confusion rather than clarity. It is by no means clear to the present reviewer, even after several readings, just what is their conception of myocardosis. They speak of it as "a designation spelling a new approach to the understanding of the earliest manifestations of coronary and myocardial insufficiency," and in many places indicate that the term applies to early changes in the heart. Yet throughout their discussion they speak of early myocardosis, and never of later or advanced myocardosis. The pain of this condition is discussed at

length, but nowhere is it made clear how it differs from that of true anginal failure. One can scarcely believe that they have justified the use of this newer term as a substitute for arteriosclerotic heart disease; with their declaration that the term "myocarditis" is no longer tenable there can be no serious quarrel.

The book is written interestingly and in many places eloquently, with a happy choice of words and descriptive phrases, but without sufficient thought of conciseness. The illustrations are uniformly excellent. The last section, devoted to the medicolegal aspects of sudden death from heart disease, is a most valuable addition to a modern text in this particular field. There is a very complete bibliography containing 1250 references, and a complete index. To me it seems a stimulating, thoughtful, and comprehensive presentation of an increasingly important subject, but one which will be of chief value to the cardiologist or the practitioner who has a special interest in diseases of the heart.

H. M. M.

DIE SOZIALE BEDEUTUNG UND BEURTEILUNG DER KREISLAUFERKRANKUNGEN. By Dr. med. Franz Grünbaum. Georg Thieme, Leipzig, 1933, pp. 128. (*Arbeit und Gesundheit*. Herausgegeben von Prof. Dr. Martineck. Heft 21.)

This small monograph deserves especial notice in the United States, for, as is manifest, it owes its inspiration to phases of interest in the heart diseases which have been cultivated especially in this country. Doctor Grünbaum has, as a matter of fact, traveled about here to be acquainted with the current course of events. The fact that his book is published in the series "*Arbeit und Gesundheit*" is evidence of the growing concern in Germany with aspects of the heart diseases from the point of view of the public health. It is, furthermore, not without interest to record the occurrence of the first meeting in Germany of the "*Wissenschaftliche Komitee zur Erforschung und Bekämpfung der Kreislaufstörungen*" in March, 1933. Leadership in interest in this problem is a development in which we may take a legitimate pride.

The specific matters which have occupied Doctor Grünbaum are statistics of mortality and morbidity in relation to age. He made comparisons between experience in the United States and in Germany and studied the relation of etiological moments to the frequency of the various groups. In arriving at diagnoses, use has been made of the classification of the New York Heart Committee. In their study of functional classification Grünbaum mentions the effort of Fraenkel and Doll who have attempted a separation based on the reactivity of patients to the intravenous injection of strophanthin. This is a method which requires further consideration but one which surely is liable to serious error. Other criteria are discussed dealing with physical examination and with efficiency—in valvular diseases and in arrhythmias.

The points of view which have received so much attention here in recent years have clearly awakened a response abroad. The importance of this newer plan of understanding the course of events of a disease as it concerns both individuals and communities will become more apparent when, as the result of sifting ideas in various countries, the effort is finally made to devise a working nomenclature of morbidity. In the development of any science, nomenclature or language is obviously fundamental. That this is being found to be the case in connection with the study of diseases is not unexpected when experience in other sciences, physical and biological, is recalled.

A. E. C.

NOUVEAU TRAITÉ DE MÉDECINE. FASCICULE X, PATHOLOGIE DE L'APPAREIL CIRCULATOIRE (CŒUR ET VAISSEAUX). Vol. I 992 pp., and Vol. II 778 pp., Masson & Cie, Paris, 1933.

This monumental work, planned by Professor Teissier but completed under the direction of Professor Lutembacher, is a compilation of most of the facts and many of the theories pertaining to the circulation. Its high quality may be judged from the names of the contributors—Lutembacher, Teissier, Prieur, Bordet, Giraud, Coste, Dumas,

Duvoir, Mouquin, Durand, Lian, Rouvière, Pichon, Béthoux and Devé. Volume I contains sections on anatomy and physiology; on the various syndromes, the arrhythmias, angina pectoris and heart failure; and on treatment and the pharmacodynamics of a large number of drugs. Volume II includes discussions of the usual and unusual diseases of the heart—pericarditis, endocarditis, myocarditis, coronary disease, congenital defects, injuries, syphilis, tuberculosis, actinomycosis, echinococcus cysts and tumors. Volume III, the section on diseases of the vessels, is still to appear.

The work is inclusive rather than selective. Each chapter is written by a man well qualified in his field, and each chapter is interesting, but on going over the work as a whole one feels that it has been impossible to avoid repetition or to preserve that balance in the discussion which will give the reader a clear sense of the distinction between the essential and the nonessential. Throughout the text there are frequent references to the literature, particularly to the French literature, but unfortunately the curious reader who wishes to look up these references will find no adequate bibliography to help him. An alphabetical index, in addition to the detailed table of contents, would add to the value of the book.

E. H.

SYPHILIS DES HERZENS UND DER GEFÄSSE. (Vol. 16 of *Medizinische Praxis, Sammlung für ärztliche Fortbildung*. Herausgegeben von L. R. Grote, A. Fromme, K. Warnekros.) By Prof. Dr. Ed. Stadler, Leitender Arzt der Inneren Abteilung des Stadtkrankenhauses Plauen i. V. Pp. 82 with 8 illustrations. Dresden and Leipzig, Theodor Steinkopff, 1932.

This brochure of eighty pages is one of a series of small volumes on medical practice intended for general practitioners. In it the experienced author presents a compact and well-balanced picture of the various aspects of syphilis of the heart and arteries. The arrangement of the book is orderly, and the pathological and clinical descriptions are concise and clear. The usefulness of the volume is increased by the comprehensive summaries placed at the end of each section and by a few well-chosen illustrations.

The greater part of the book is, very properly, devoted to syphilis of the aorta, and this subject is treated with admirable clarity and thoroughness. Much attention is given to a consideration of the treatment of aortic aortitis, with insistence upon the necessity of prolonged, thorough antiluetic therapy, including the arsenicals, even in cases complicated by aortic insufficiency and by anginal pain. Emphasis upon the need of caution and judgment in the use of the arsphenamines, however, is not lacking.

No attempt is made to furnish a complete bibliography, but a list, predominantly German, of the more important recent writings upon the subject of cardiovascular syphilis is appended.

As an epitome of our present knowledge of this vastly important subject the volume merits cordial commendation.

L. A. C.

RESULTATS DU TRAITEMENT CHIRURGICAL DE L'ANGINA DE POITRINE RÉCUEIL DE 54 OBSERVATIONS DE METHODE DE LA SUPPRESSION DU REFLEXE PRESSEUR ET DE 82 OBSERVATIONS DE SYMPATHECTOMIE AVEC GANGLION ÉTIOLE. Par D. Danielopolu. Pp. 285, with 8 figures. Bucarest, Impr. Cultura, 1932.

The monograph is based upon a careful analysis of the surgical treatment of the cases of angina pectoris; 52 according to the Danielopolu method (suppression of the pressor reflex) and 82 with removal of the stellate ganglion, according to the method of Franek-Ionneseo-Gomoiu.

Danielopolu calls his method that of the suppression of the pressor reflexes. He advises the resection of the cervical sympathetic chain, without removal of the stellate ganglion but with section of the fibers of the cervical vagus which enter the thorax, and sections of the vertebral nerves, and of the communicating branches which unite the inferior cervical ganglion and the first thoracic to the sixth, seventh, and eighth cervicals

and the first dorsal roots. Operation is first performed on the left side and then if necessary, on the right. Even if the radiation of pain is to the right side, the operation is performed on the left side as the left ventricle is assumed to be the site of origin of the pain. Ether is the anesthetic of choice. Of the 54 cases operated upon according to the principle of Danielopolu, 70 per cent were greatly relieved or cured for a period of from three months to one year, while only 51 per cent, in 82 cases in which the stellate ganglion had been removed, were relieved or cured. There were 22 per cent of failures with the author's method and 33 per cent with that of Franek-Ionesco-Gomoin. The operative mortality was very much lower in the former, being 1.8 per cent, and in the latter 17 per cent.

The value of any therapeutic procedure depends upon the accuracy of the anatomical diagnosis. The reviewer is unable to determine the type of case for which the author advocates surgical interference.

Anatomically the author classifies as centripetal cardio-aortic nerve trunks; the centripetal fibers passing through the stellate ganglion to the second, third, and fourth dorsal vertebral roots, the vertebral nerve, the cervical sympathetic, and the pressor and depressor fibers of the vagus passing to the inferior cervical ganglion. He maintains that the centripetal fibers passing to the second, third, and fourth dorsal roots are pressor, and excitation of the medullary end causes a rise in blood pressure in the majority of cases. The vertebral nerve, on excitation, based upon experiments in 8 dogs and 3 cats, gives pressor effects. The cervical sympathetic chain has both pressor and depressor effects. The branches from the vagus nerve have also pressor and depressor effects.

The pressor phenomena are defined as an exaggeration of the predominant factors of the cardiovascular mechanism: automatism, excitability, conductivity, and cardiac and vascular contractility. Depressor phenomena are defined as a diminution of any or all of these properties.

The centripetal fibers, through their connections with the cerebrospinal system, convey sensitivity and thus the sensation of pain is felt. The hypothesis assumes that the toxic products of fatigue accumulate in the myocardium due to a disproportion between the work done and the coronary flow. A pressor reflex results and this pressor reflex increases the burden of work on the heart. This increases the intoxication which results in motor and sensory phenomena which we call angina. The author then states: "To prevent angina we must cut the centripetal paths of the pressor reflex." The author definitely states that the sympathetic fibers passing through the stellate ganglion to the coronary vessels are vasodilatory and that the parasympathetic fibers passing through the vagus are vasoconstrictors. If one accepts this statement, then the removal of the stellate ganglion destroys the nerve trunks which cause dilatation of the coronary vessels. This is the author's thesis, and is his main argument against the operation of Franek-Ionesco-Gomoin, and also against the school of Leriche and Fontaine. Page after page reiterates this and each individual case is analyzed on this basis. The cause of immediate and remote death following the operation is believed to be due to this fact. The author further states that the destruction of the vasodilatory fibers increases the "myocarditis" of angina. It is somewhat difficult to see how this quite fits the theory or to know what the author means by "myocarditis" of angina.

The anatomical researches of Ranier and H. Dumitresco are important. They made careful dissections of the sympathetic nervous system on twelve cadavers and twenty-five fetuses. Their general conclusions are as follows: The stellate ganglion is composed of three parts: intermediary, cervical, inferior, and first thoracic. It can be either a single mass caused by the fusion of the three, or in two parts: an antero-internal situated before the vertebral artery which is the internal ganglion, and the posterior-external formed from the cervical inferior and the first thoracic, or it may consist of two cervical and by the first thoracic alone.

The intermediary ganglion gives off the important cardiac inferior nerves. Extirpation of this ganglion is a partial stelletomy. The cervical inferior ganglion gives off several cardiac inferior nerves, more than that of the first thoracic. Extirpation of this ganglion is therefore a partial stelletomy. The middle cervical ganglion may be lower and be in two parts and may be mistaken for the intermediary ganglion. The vertebral nerve practically always arises from the superior pole of the inferior cervical ganglion. Therefore extirpation of this ganglion must destroy the vertebral nerve.

This monograph is a contribution to the study of the physiology of the sympathetic nervous system and of the innervation of the heart. The dissection of the anatomists and the illustrative drawings of the sympathetic and parasympathetic nervous system with their connections to the central nervous system are rather schematic, and if subsequent work substantiates the anatomical facts, further physiological experiments are needed to prove the many contentions of the author.

The value of the surgical treatment of the pain syndrome of angina is still uncertain. In general there is less enthusiasm for the operative treatment of angina pectoris than at the time the method was originally proposed. The author does not comment on the method of paravertebral block anesthesia as originally proposed by Swetlow. This method appears to be safer and is at least associated with practically no mortality. The surgery of the sympathetic nervous system is still in its early stages, and the reviewer feels that much more must be learned before one can be partisan in the many controversial matters concerning the anatomy, physiology, and pharmacology of the vegetative nervous system.

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DYNAMIC DILATATION OF THE THORACIC AORTA*

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DYNAMIC dilatation of the aorta may be defined as an increase in the size of the lumen for a variable distance along its course, without structural disease of the aortic wall. The systolic excursion of the aorta is usually increased. The enlargement is ordinarily maintained throughout diastole, and is thought to be the mechanical result of cardiovascular factors. It must be understood that disease at the site of dilatation does not exist to an influential degree or the condition at once becomes confused with aneurysm, aortitis or arteriosclerosis.

Osler¹ stated that dynamic dilatation of the aorta was first observed in the time of Morgagni, and describes its occurrence in three conditions: aortic insufficiency, neurotic states, and anemia.

In 1886 Hare² reported a most instructive case as aneurysm of the thoracic aorta. A white girl, aged eighteen years, came under his observation complaining of pain in the left chest and arm. She had suffered from attacks of acute articular rheumatism every winter for six or seven years. "Inspection of the chest showed an egg-shaped protrusion in the suprasternal notch, very expansile and bulging at each systole of the heart. Dilatation extended well up the innominate artery for over one inch from its point of origin. . . . Over the protrusion was a thrill and bruit." There was a double aortic murmur and a water-hammer pulse. Osler, who saw the patient during life, stated that at autopsy a few months later, he was not surprised at finding the lumen of the aorta too small to admit the index finger.

Sheldon³ observed the condition in a boy, ten and one-half years old, who suffered from chronic nephritis with hypertension and secondary anemia. The blood Wassermann test was negative on two occasions. The systolic blood pressure was 210 mm. Hg; the diastolic, 155 mm. Hg.

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An aortic diastolic murmur developed while the patient was under observation. Roentgen-ray studies demonstrated pronounced enlargement of the aortic arch. The child died of uremia a month later. Autopsy showed an aortic arch of normal size. Sheldon cites a similar case described by Evans;⁴ this patient, a child, died of cerebral hemorrhage. These three cases are unquestionable examples of dynamic dilatation of the thoracic aorta. Navarrow⁵ in 1917 reported a probable case. The patient was a child with rheumatic aortic insufficiency. Syphilis was excluded. Under observation the aortic arch dilated from a position 1 cm. to a position 3 cm. above the suprasternal notch. Navarrow suggested that rheumatic disease may affect the aorta as does syphilis.

Compare with this group the cases of permanent enlargement of the cavity of the aorta, due to syphilis and arteriosclerosis reported by McCrae,⁶ Brown,⁷ and Lankford.⁸ This condition most commonly involves the ascending aorta. It was described by Hodgson in 1815 and is referred to as the *Maladie de Hodgson* by the French. Unlike dynamic dilatation it is due to disease of the aortic wall, either arteriosclerosis or syphilis, or both. The disease process frequently involves the aortic valve. Until the advent of the x-ray this type of aortic enlargement was almost always an unsuspected finding in the dead house. With modern x-ray methods its detection is common. As might be suspected the patients are almost without exception over thirty-five years of age. Two of McCrae's cases were under thirty years of age, and, therefore, may not have belonged to this group. The enlargement is of fusiform character and involves the arch of the aorta and is always in evidence at autopsy with accompanying disease of the vessel wall.

CASE REPORTS

The three following cases were studied on the wards of the University of Michigan Hospital. All were seen within a period of two months.

CASE 1.—A housewife, white, aged thirty years, was admitted to the medical ward Jan. 8, 1932, complaining chiefly of pain in the precordium and in the right side. These pains were not associated, the latter being felt in the right costo-vertebral angle. She was known to have had a "leaking heart" at the age of twelve years. At fifteen years she had a typical attack of rheumatic fever. She thought that this aggravated the heart condition, as at that time she experienced shortness of breath on exertion. The precordial pain, although present for the past eight years, had become more severe during the past year. It was most intense at the apex of the heart. Its onset was sudden and was accompanied by numbness of the left arm, tachycardia and flushing of the face and neck. She had noticed edema only during pregnancies. She was the mother of four children and had had considerable domestic difficulty.

Physical Examination.—The patient was asthenic and did not appear acutely ill. There was no orthopnea or dyspnea at rest. The pupils were round, regular, equal, and reacted to light and in accommodation. The apex impulse was seen and felt in the fifth intercostal space, 7.5 cm. from the midsternal line. It was well localized and not abnormally forceful. There was visible systolic pulsation

in the right second intercostal space just lateral to the sternal border, more pronounced during full expiration and after exertion. It was not palpable and there was no thrill. At this level the supracardiac dullness extended 4 cm. to the right of the midsternal line. The left border of cardiac dullness extended 8 cm. to the left of the midsternal line in the fifth intercostal space. A soft systolic murmur was heard at the apex. In the aortic area was a high-pitched diastolic murmur of medium intensity which replaced the second sound. The pulmonic second sound was not accentuated. The systolic blood pressure was 138 mm. Hg; the diastolic, 72 mm. There was no Corrigan pulse, nor were there other vascular signs of aortic insufficiency. The lungs were clear. There was tenderness in the right costovertebral angle. The right kidney was palpable and movable.

Laboratory Tests.—The routine Kahn test for syphilis was negative on two occasions. The routine urine, blood, and stool examinations showed nothing abnormal. The electrocardiogram showed marked left ventricular preponderance. The x-ray studies, including fluoroscopic examination, showed a gross increase in



Fig. 1.—Case 1. Pronounced increase in the supracardiac shadow, due to dynamic dilatation of the aorta in a case of aortic insufficiency (probably rheumatic in origin). Boundary of aortic shadow marked by arrows.

the anteroposterior diameter, as well as in the transverse diameter (Fig. 1) of the ascending aorta without cardiac enlargement. The transverse and descending portions of the aorta were thought not to be dilated. The patient had no attacks of chest pain during the four weeks that she remained on the medical ward, although she was up and about during the last half of this period. She returned three months later for a check-up. No drugs had been taken in the interim. Further x-ray studies at this time showed no change in the size of the heart or aorta.

Discussion.—Syphilis with aortitis and aneurysm and rheumatic heart disease were the cardiovascular diagnoses considered. It was apparent clinically that a large part of the precordial pain was psychogenic. The patient apparently desired hospitalization to escape domestic routine. The only "heart attack" occurred in the convalescent hospital pending discharge from the surgical service where the diagnosis of nephroptosis

had been made. The pain of syphilitic aortitis is usually substernal rather than apical and is not as a rule accompanied by rapid heart action. Under the fluoroscope the lively pulsations of the first part of the aorta were striking. The enlargement apparently involved the entire circumference of the vessel. When the pulsation of an aneurysm is visible, it is usually palpable as well. Since the patient was known to have a valve lesion at twelve years of age, it is improbable that syphilis could have been the causative factor. The definite history of rheumatic fever strongly suggests that this condition was alone responsible for the lesion. Rheumatic aneurysm is relatively rare, and it is of the mycotic type which is quite incompatible with the picture presented. In view of the observations described later, it seems probable that the dilatation of the aorta was of the dynamic variety, and one would not expect to find the vessel enlarged post mortem.



Fig. 2.—Case 2. Dynamic dilatation of the aorta and pronounced enlargement of the heart, involving the left ventricle particularly. Limits of aortic shadow marked by arrows; the point indicated pulsated violently on fluoroscopic examination, and aneurysm was suspected.

CASE 2.—A boy, aged fourteen years, was admitted to the medical ward on Feb. 8, 1932, complaining chiefly of a head cold. Head colds and sore throat had occurred frequently for several years. At the age of eight he was told he had heart disease. His activities had been restricted since. The present respiratory infection had troubled him for four weeks and was accompanied by sore throat and fever. There was no history of rheumatic fever or chorea.

Physical Examination.—The patient was delicately built, well nourished, and not acutely ill. The pupils were equal and reacted to light and in accommodation. There was slight pulsation of the retinal arteries. There was considerable carotid pulsation at the angles of the jaw. The neck veins were not distended. Systolic pulsation was seen in the suprasternal notch and in the right second intercostal space close to the sternum. The apex impulse was in the anterior axillary line at the level of the fifth intercostal space. The left border of cardiac dullness was 13 cm. and the right border 3.5 cm., from the midsternal line. The

supracardiac dullness measured 7 cm. in width. There was a thrill at the apex and base. A double aortic murmur was present. At the apex there was a loud harsh systolic murmur and an early diastolic rumble. The pulmonic second sound and the mitral first sound were accentuated. The rhythm was regular. The heart rate was 104 per minute. The systolic blood pressure was 130 mm. Hg; the diastolic 40 mm. Hg. There was a suggestive Corrigan pulse, and a pistol-shot sound was audible over the femoral vessels. The lungs were clear. The abdomen and extremities were negative. The reflexes were active.

Laboratory Tests.—The routine Kahn test was negative. The blood, stool, and urine studies showed nothing abnormal. The electrocardiogram showed extremely tall QRS deflections. The T-waves were diphasic in Lead II and inverted in Lead III, as is frequently the case in aortic insufficiency with great cardiac enlargement. The orthodiagram showed a variation of plus 30 per cent in the frontal plane area (as compared with the normal for individuals of similar height and weight), and plus 39 per cent in the transverse diameter of the cardiac silhouette. X-ray studies (Fig. 2) showed gross prominence of the aortic knob and widening of the ascending aorta; cardiac enlargement, chiefly left sided; and thickening of the apical pleura on the right side. Lateral plates confirmed the diagnosis of aortic dilatation.

Clinical Course.—The patient remained in the hospital four weeks on bed rest. There was slight fever and leucocytosis, possibly due to active endocarditis. Prolonged rest was advised on discharge.

Discussion.—The aortic dilatation in this case was more diffuse than that in Case 1 and involved the entire aortic arch. On fluoroscopic examination the size and pulsations of the aorta were striking. The examiner's first remark was "aneurysm." The marked enlargement of the left ventricle is apparent in the x-ray plate (Fig. 2).

CASE 3.—A white boy, aged seventeen years, was admitted to the medical service on Feb. 11, 1932, complaining chiefly of shortness of breath and pounding of the heart. There was a history of rheumatic fever six years before. No history of congestive cardiac failure.

Physical Examination.—The boy was fairly well developed, but his nutrition was poor. The cheeks presented a malar flush and the lips a reddish cyanosis. The left pupil was slightly larger than the right. There was moderate overdistention of the veins of the neck and vigorous throbbing of the carotid arteries. The precordium was prominent and the cardiac apex pounded forcibly in the midaxillary line. All the classical signs of mitral stenosis and aortic insufficiency were present. The supracardiac dullness extended 7.5 cm. to the right of the midsternal line at the level of the second intercostal space. In this space there was a visible systolic pulsation followed by a diastolic thrill. The rhythm was regular; the heart rate 100 per minute. The systolic blood pressure was 120 mm. Hg, the diastolic 40 mm. The lung fields were clear. The liver border reached two finger breadths below the right costal margin. The remainder of the examination contributed nothing of importance.

Laboratory Tests.—The routine blood Kahn test was negative. The blood, stool, and urine findings were not abnormal. The electrocardiogram showed marked inversion of the T-waves in Leads I, II, and III, suggesting myocardial changes. X-ray studies (Figs. 3 and 4) showed widening of the thoracic aorta and prominence of the soft tissues of the neck, suggesting involvement of the innominate, common carotid and subclavian arteries as well. The orthodiagram showed a plus 48 per cent variation in the frontal plane area (in comparison with normal stand-

ards for individuals of like height and weight) and a plus 47 per cent variation in the transverse diameter of the cardiac silhouette.

Clinical Course.—The patient remained in the hospital four weeks. The systolic blood pressure varied from 100 to 120 mm. Hg, the diastolic rose steadily from 40 mm. Hg on admission to 80 mm. at the time of discharge.

Discussion.—The general picture resembled that seen in Case 2 in many respects. One might even have mistaken it for a more advanced stage of the underlying process in the same individual. The dilatation of the aortic arch was extreme. The right border of the ascending aorta lay just inside the right midclavicular line. There were no symptoms of superior mediastinal compression. It is interesting to speculate on the possibility that the left pupillary enlargement resulted from stimulation of the left thoracic sympathetic nerve trunk by the large vigorously pounding thoracic aorta. More interesting still was the

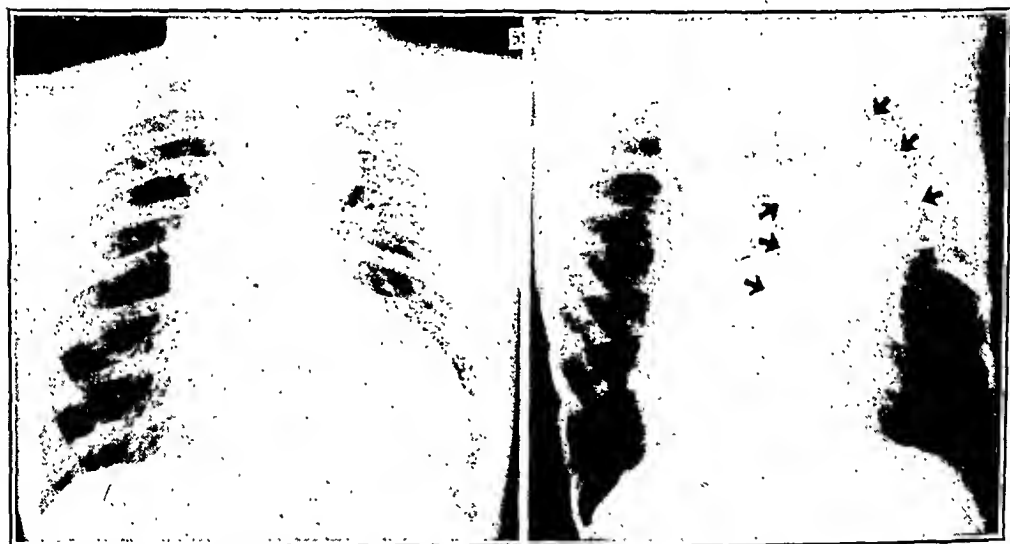


Fig. 3.

Fig. 4.

Fig. 3.—Case 3. Dynamic dilatation of aorta and its main branches. Great enlargement of heart.

Fig. 4.—Case 3. Cardiac silhouette, right anterior oblique view. Outline of enlarged ascending aorta indicated by arrows.

steady rise of the diastolic blood pressure during hospitalization. Surely such mechanical improvement could not have been due to actual healing of the pathological changes in the aortic valve, for such healing ordinarily results in greater insufficiency or stenosis. It seems probable that the steady rise of 40 mm. Hg in the diastolic pressure was due to improvement of a superimposed relative insufficiency of the aortic valve, associated with the extreme aortic dilatation.

OTHER CASES OF RHEUMATIC AORTIC INSUFFICIENCY

Eighty cases of rheumatic aortic insufficiency were selected from the hospital records for study. In order to avoid including examples of luetic or arteriosclerotic aortic insufficiency unwittingly, all cases in

which the patient was more than thirty-one years of age were excluded.

Syphilitic aortic disease is rare in the age interval with which we are concerned. In the past seven years no cases of syphilitic aneurysm have been observed in this hospital in which the patient's age was less than thirty-one years. This condition has been observed in patients less than thirty-five years of age only six times during the same period. In all of these patients serological tests for syphilis were positive, and there was a history of syphilitic infection or of symptoms suggesting it. In all instances precordial pain was the chief complaint.

In 98.8 per cent of the eighty cases of rheumatic aortic insufficiency studied, the additional clinical diagnosis of mitral stenosis had been made. All of the patients had x-ray studies, and all gave negative serological tests for syphilis. Eight and four-tenths per cent were found to have definite enlargement of the aortic arch. Twenty com-



Fig. 5.—Cardiac silhouette in a case of rheumatic aortic insufficiency in which a hypoplastic aorta was found post mortem. The borders of the aortic shadow are indicated by arrows.

plained of pain that could be ascribed to cardiovascular disease. The pain seemed to be dependent upon the grade of heart failure. No patients complained of severe, unbearable pain who were not on the verge of advanced congestive heart failure. Pathological studies in cases in which death occurred during an acute attack of rheumatic fever have shown that acute rheumatic aortitis is present in the majority.¹⁰ Precordial pain is not a usual complaint of patients weathering an acute rheumatic attack unless pericarditis or pleuritis develops. It would seem that acute rheumatic aortitis does not commonly produce pain. It is fairly well established that rheumatic disease of the aorta is confined chiefly to the adventitia with minute intimal changes.¹¹ The media, though affected during the acute stage, undergoes no changes even remotely resembling those of syphilis. It is for this reason that rheumatic aneurysm is invariably of the mycotic type.

In this group of eighty patients the average systolic blood pressure was found to be 129 mm. Hg; the average diastolic was 71 mm. The heart rate was so variable that an average would mean little or nothing. Only 64 per cent of the patients with an enlarged aorta had a pulse pressure greater than the average. In this series of cases of rheumatic aortic insufficiency there was one with clinical enlargement of the aorta (Fig. 5) that came to autopsy. The aorta was found to be hypoplastic post mortem.

The healing of the acute aortitis that must accompany most of the severe cases of rheumatic fever is apparently complete in the vast majority. This is shown by a study of 64 autopsied cases of rheumatic heart disease, only one of which showed microscopic evidence suggesting rheumatic aortitis. This series of autopsied cases, included cases with either aortic or mitral lesions or with both. In no instance was the aorta enlarged. Nineteen per cent of the patients with aortic insuf-

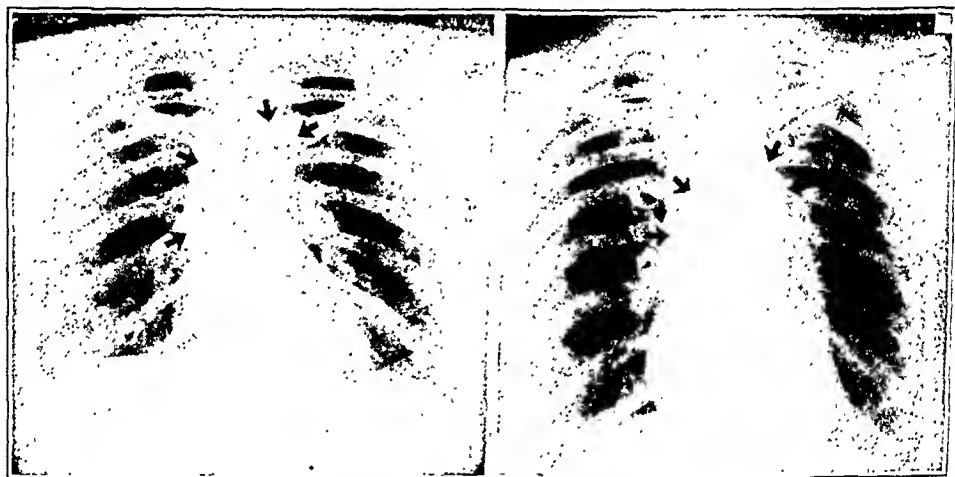


Fig. 6.

Fig. 7.

Fig. 6.—Dynamic dilatation of the aorta in a patient with cardiac symptoms attributed to a psychoneurosis.

Fig. 7.—Dynamic dilatation of the aorta in a young psychoneurotic patient. Outline of aorta indicated by arrows.

ficiency with or without mitral stenosis had hypoplasia of the aorta. A clinical diagnosis of aneurysm was made in 3 per cent of the cases, and in each instance aortic insufficiency was present. In no case was an aneurysm found post mortem. It was rather interesting to note that 16 per cent of the cases diagnosed clinically as having aortic insufficiency and mitral stenosis were shown after death to have aortic insufficiency without organic mitral stenosis.

EXOPHTHALMIC GOITER

Two hundred and sixty-three cases of exophthalmic goiter were selected. There was no evidence that any of the patients had syphilis. All were between fourteen and thirty-one years of age. All had had x-ray studies. It was found that 12 per cent had enlargement of the

aortic arch. Of this number only one complained of pain that could be attributed to heart disease.

The aortic enlargement in this group was not as striking as in the rheumatic group. Prominence of the aortic knob was the common finding, although widening of the base of the aorta and violent pulsations were observed on a few occasions. The average pulse pressure was 72 mm. Hg. One of the patients with clinical enlargement of the aorta died of pneumonia, and the aorta was hypoplastic at autopsy.

CARDIAC NEUROSIS

The case records of thirty-one patients between fourteen and thirty-one years of age with cardiac complaints that were attributed to a psychoneurosis were examined. In none of these cases was there any evidence of syphilitic infection. Roentgen-ray examinations had been made in all. In three, or 9 per cent, there was definite enlargement of the aortic arch as determined by x-ray and fluoroscopic examination. (Figs. 6 and 7.) Two-thirds of the total number of patients complained of precordial pain. Aside from pain, sinus tachycardia was the only cardiovascular symptom. The electrocardiogram showed nothing abnormal except rapid heart action. The basal metabolic rates were all within the average normal limits. Foci of infection were not in evidence.

DISCUSSION

The literature on the subject of dynamic dilatation of the aorta was found to be surprisingly scanty; the condition is not well understood. It would seem that enlargement of the aortic arch is not uncommon in young persons affected with rheumatic aortic insufficiency, exophthalmic goiter, or a cardiac neurosis. That it also occurs in young persons with chronic nephritis and hypertension is shown by Sheldon's case already mentioned. On a few occasions I have observed striking enlargement of the aortic arch in a young person with pulmonary tuberculosis.

Dynamic dilatation of the aorta appears to depend upon various alterations in cardiovascular dynamics, but the exact manner in which it is brought about is not clearly understood. The age of the patient, sinus tachycardia, an increase in pulse pressure, an increase in the force and in the quantity of blood ejected by left ventricular systole and an increase in peripheral resistance are all thought to be important factors. Nutritional and toxic states may play a part in its development.

CONCLUSION

In young individuals an alteration in the normal cardiovascular dynamics may bring about an enlargement of the aortic arch. The enlargement may be pronounced and may induce a relative insufficiency of the aortic valve. In patients with a cardiac neurosis the dilated

aorta has been observed to return to normal size within a few weeks.¹² This so-called dynamic dilatation is manifest clinically, but not at autopsy. The condition is far more common than the literature would indicate, and is of great importance because of the frequency with which it is mistaken for aneurysm. Aortic enlargement of this type is commonly labeled aortitis, although no inflammation or organic disease of the vessel exists. The term aortitis so used is therefore misleading. In older people with aortic dilatation the diagnosis of aortitis is usually correct, for here autopsy reveals fusiform enlargement and degenerative changes. When syphilitic infection is known to have occurred and sub-sternal pain, paroxysmal nocturnal dyspnea and a ringing aortic second sound are present, the diagnosis of aortitis may be justified even when x-ray examination is negative.

One should hesitate to make the diagnosis of aortitis or aneurysm in young individuals simply because the aorta is enlarged; the enlargement is likely to be of the dynamic sort.

Thanks are given to Dr. Frank N. Wilson for his invaluable assistance.

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A STUDY OF LEAD IV

ITS APPEARANCE NORMALLY, IN MYOCARDIAL DISEASE, AND IN RECENT
CORONARY OCCLUSION*†

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WOLFERTH and Wood¹ recently described a fourth lead with which they found changes diagnostic of coronary occlusion that were absent in the three-lead electrocardiogram. This work shows that important electrocardiographic changes may be missed because they occur in the anteroposterior diameter, which the ordinary leads do not explore. In a second report, Wolferth and Wood² added three further cases of coronary occlusion in which the fourth lead was not essential for the diagnosis, and in one of which the fourth lead was not abnormal.

We decided to study this fourth lead further in order to define the normal configuration and the deviations from normal which might occur in a series of unselected consecutive cases. In this way we hoped to determine the value of using the fourth lead routinely.

Various tri-dimensional leads have been used experimentally (Cohn,³ Wilson,⁴ Zeisler and Katz⁵) but we decided to follow the Lead IV already studied by Wolferth and Wood.¹ Any other fourth lead which tapped the heart current in the anteroposterior plane would have served as well, but at this time it would be confusing to use another lead when a standard had been established. Indeed, in following their procedure we were tempted to reverse the connections of the electrodes because the normal configuration of Lead IV so taken, is like that of the other leads.

A series of 25 normals was obtained for control. Then, during June, 1932, this lead was used routinely on 86 patients with clinical evidence of heart disease, who were sent to the Heart Station for electrocardiograms. In addition, tracings of 11 patients with recent coronary occlusion were taken, in one of whom the diagnosis was confirmed by necropsy.

The series of tracings is too small to draw final conclusions on many points. We feel justified in presenting our tentative conclusions to serve as a basis for the normal and for deviations from normal. It will be seen, however, that the material is adequate to settle many points.

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†From the Heart Station, Michael Reese Hospital, Chicago.

TECHNIC

The technic of Wolferth and Wood¹ was modified slightly. The patient lay on his left side. Pliable pure tin electrodes, 3 cm. by 8 cm., were employed. The site of the electrodes was shaved when necessary. The skin over the region was cleansed with alcohol. A warm paste of flour and salt was spread over the electrodes, which were then quickly applied to the chest. The anterior electrode was placed at the level of the fourth interspace just to the left of the sternum. The posterior electrode was placed on the back directly opposite the anterior electrode, viz., 180° from it, just medial to the right scapula. The anterior electrode was connected to the right arm terminal and the posterior electrode to the left arm terminal of the control box. The plates were kept close to the body, either with pillows or an elastic webbing.

The small size of the electrodes made it necessary to use precautions to keep the skin resistance low, by brightly polishing the electrodes, removing greasy material from the skin, increasing local circulation with warmth, making close contact with the skin and by using a concentrated salt-flour paste. Even with these precautions a few of our tracings showed overshooting. We discarded all tracings which showed, when standardized, an overshooting of more than 1.5 mm.

Our cases fell into three groups: (1) those showing no evidence of heart disease clinically or electrocardiographically (in the ordinary three leads); (2) those with clinical evidence of cardiac disease (a) with normal configuration in the standard three leads, (b) with abnormalities in these three leads indicating myocardial damage; and (3) cases of recent coronary occlusion. The appearance of Lead IV in each of these groups will be described in turn. The description is based on a detailed analysis of a large summary table of the measurements of all four leads in each case of the series.

NORMAL APPEARANCE OF LEAD IV

The Lead IV of the individuals who had no manifest cardiac pathological condition and whose three-lead electrocardiogram was normal, showed the following (Table I): (1) The P-wave was usually negative, often notched, and occasionally diphasic. (2) The P-R interval was generally shorter by 0.01 to 0.03 sec. than in Lead II (the usual lead in which the P-R is measured). (3) The QRS was diphasic, the first phase being negative, or if one prefers, a Q-wave in the sense of Pardee.⁶ The QRS was high as a rule (average 20 mm.). The relative magnitude of the two phases of QRS varied considerably. In no instance was the QRS entirely negative or positive; as a rule the smaller phase was more than 15 per cent of the larger, and usually the two were of equal magnitude. In no instance was the first phase of the diphasic QRS positive. As a rule there was slight slurring of the downstroke of the Q-wave and of the positive wave. (4)

The S-T segment was usually isoelectric, but sometimes it was depressed as much as 2 mm. It was never elevated. Often the S-T interval could not be definitely distinguished, for the T-wave took off directly from the QRS. The S-T segment in many cases was curved. (5) The T-wave was inverted, as a rule, often peaked, with symmetrical sides

TABLE I
ANALYSIS OF LEAD IV IN 25 NORMAL CASES

	AVERAGE	LEAST	GREATEST
Height of P	$-\frac{3}{4}$ mm.	$+\frac{1}{2}$ mm.	$-1\frac{1}{2}$ mm.
Duration of P	0.08 second	0.04 second	0.12 second
P-R interval	0.155 second	0.12 second	0.20 second
QRS duration	0.08 second	0.07 second	0.09 second
Amplitude QRS*	20 mm.	5 mm.	34 mm.
Height of Q	$-8\frac{1}{2}$ mm.	-1 mm.	-19 mm.
Height of positive portion of QRS	+12 mm.	+2 mm.	+33 mm.
Height of T	-3 mm.	+1 mm.	-8 mm.
Duration of T	0.18 second	0.07 second	0.25 second
S-T deviation	-1 mm.	0 mm.	-2 mm.

*Amplitude of QRS is the sum of the amplitudes of its two phases.

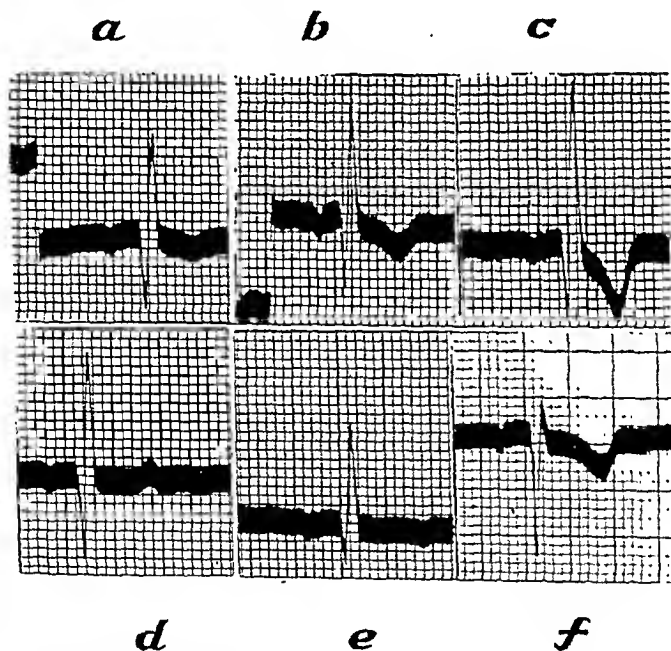


Fig. 1.—Six examples of normal Lead IV to show the range of variations in the QRS complex and in the T-wave.

and rounded shoulders, the convexities pointing upward and toward each other; an appearance which resembled the inverted coronary T-wave. In one case the T-wave was small and diphasic. (6) Occasionally an inverted U-wave was present. (7) The durations of P, QRS, and QRST in Lead IV were identical, within 0.02 to 0.03 of a second, with the meas-

urements in the other three leads (cf. Zeisler and Katz⁵). Segments of Lead IV in six normal cases are shown in Fig. 1.

LEAD IV IN PATIENTS WITH EVIDENCE OF CARDIAC DISEASE

The analysis is based on 86 tracings of all four leads in patients with evidence of heart disease other than recent coronary occlusion. Only 33 of these 86 records of Lead IV showed characteristics differing from the normal standards given above—the rest presented no deviation from normal. In general, our analysis showed that when the electrocardiogram of the three leads was within normal limits, it was also normal in Lead IV; when the curves of the standard three leads were abnormal, Lead IV was abnormal. A sufficient number of exceptions were present to warrant further analysis.

The time relationships are the same in Lead IV as in the other leads, viz., the duration of the P, the QRS, and the T in Lead IV, was found to be the same as in the other three leads. Two cases of bundle-branch block, for example, showed the identical widening of the QRS complex in all four leads. The P-R interval in first degree A-V block was also increased in Lead IV.

The arrhythmias, auricular fibrillation, A-V block, intraventricular block, sinus arrhythmia and shifting pacemaker, showed up as well in the fourth lead as in the conventional three. The "f" waves of auricular fibrillation were not always clearer in the chest lead than in the other leads (cf. Lewis⁷). In one instance Lead IV showed sino-auricular block when the others did not. It is likely that this phenomenon is due to the different position of the patient during the recording of Lead IV. The same explanation probably holds for those cases in which extrasystoles appeared in Lead IV but not in the other three leads.

Changes in QRS.—For this study the amplitude of the QRS complex was considered as the sum of the maximum deviation above and below the isoelectric line. The amplitude of the QRS complex so measured in Lead IV bore no definite relation to the amplitude in the other leads in this group of cases and in the normal series. Usually the amplitude in Lead IV was higher than in Leads I, II, III, but sometimes the reverse was true. "Low voltage" of the QRS in the conventional leads was not always accompanied by a "low voltage" in Lead IV as shown in Table II; the deflection often being normal, or even exceptionally high in this lead. Two tracings in our series showed a low deflection of QRS in Lead IV with deflections of normal amplitude in Leads I, II and III. These observations are summarized in Table II, in which QRS heights in Leads I, II and III of less than 10 mm. are compared with the QRS amplitude in Lead IV, and amplitudes of QRS of less than 10 mm. in Lead IV are compared with the amplitudes in the other leads. This lack of correlation is not difficult to understand. It has been pointed out (Katz⁸) that low amplitude in the standard three leads may be due to one of three causes: (a) intraventricular block, (b)

relative increase in the shunting of the heart's currents away from the electrodes, and (c) a change in the heart's position so that its long axis lies in a plane more nearly perpendicular to the plane of the leads. It is likely that the change in the position of the heart explains the lack of correspondence of the amplitude in Lead IV to that in the ordinary three leads. Lead IV may therefore be useful in separating cases of "low voltage" in the standard leads due to change in position, from those due to intraventricular block or increased body shunting.

TABLE II
CORRELATION OF AMPLITUDES* OF QRS IN THE FOUR LEADS

LEAD I	LEAD II	LEAD III	LEAD IV
11 mm. 16 11	7 mm. 6 8	8 mm. 12 4	3 mm. 4 9
4 5 5 6 4 7 3	5 5 4 5 8 7 7	5 2 2 3 7 2 5	8 8 6 9 6 10 10
4 1 4 4 6 4 5 3 7 8 3 6 7 6 6 6 5	4 5 2 3 7 6 5 9 8 8 9 4 7 5 3 3 9	2 3 3 5 4 2 6 5 2 4 6 3 8 7 7 8 4	15 11 15 14 19 13 14 16 19 16 16 17 16 18 15 18 14
5 6 4 8 7 7 9 8 8 8 3 8 4	4 3 8 5 9 5 5 9 7 3 8 8 3	5 5 6 6 3 6 4 7 5 6 6 3 9	20 21 43 22 36 24 41 27 20 21 22 21 21

*Amplitude of QRS is the sum of the amplitudes of its two phases.

Some slight slurring was present almost regularly in the routine Lead IV. The downstroke of the initial negative deflection and the downstroke of the terminal positive deflection were of less steep gradient and thicker than the upstroke. Occasionally an abnormal degree of slurring, or even notching, appeared in Lead IV without a similar change in the ordinary leads. More often, however, slurring or notching appeared in either Lead I or II but not in Lead IV. In a few instances we found excessive slurring and notching in all leads. In other words, excessive slurring might appear in Lead IV when not present in the other leads, and it might be absent in Lead IV when present in the other leads. Notching and slurring in Lead IV, but not in Leads I or II, occurred six times. In all of these there were clinical evidences of myocardial disease. Slurring or notching of Lead IV as an isolated finding therefore suggests cardiac disease; but no more significance can be attached to it than to isolated slurring or notching of QRS in either Leads I or II.

In no instance of this series was the first phase of a diphasic QRS upward. A small triphasic QRS (only 3 mm. in height) was found once, associated with other electrocardiographic evidence of myocardial damage, viz., notching and slurring of all the leads, an inverted T-wave in Leads I and II, and a negative S-T in Leads I, II and III. In three cases the QRS was monophasic, being exclusively upward. In each of these cases there was other electrocardiographic evidence of myocardial disease, such as a negative T-wave in Leads I or II, slurring and notching of QRS in these leads, "low voltage" (below 5 mm.) in all three leads, or deviations of the S-T segment.

There was no correlation between a deep Q-wave in Lead III (or Leads II and III) and the form of the QRS complex in Lead IV. Nor was there any correlation between the deviation of the electrical axis in the three leads and the form of the QRS complex in Lead IV. Left axis deviation (or left ventricular preponderance) might be associated in Lead IV with a higher positive phase of the diphasic QRS, with a higher negative phase, or with phases of approximately equal magnitude. No instance of right axis deviation was recorded in this series.

T-Wave.—A positive T-wave in Lead IV occurred 16 times. Eleven of these 16 tracings were cases in which the three conventional leads showed changes characteristic of myocardial disease, such as inverted T-waves in I and II, slurring and notching of QRS in I or II, and deviation of the S-T segment. But five of these tracings were from patients whose three-lead electrocardiogram showed no abnormalities. These five patients were as follows: (1) a woman of fifty years with hypertension and an enlarged heart in the roentgenogram; (2) a boy of five years with acute rheumatic fever; (3) a mentally retarded boy of thirteen years with cryptorchidism and with a systolic apical thrill and murmur which may have been due to congenital heart disease or a previously unrecognized attack of acute rheumatic fever; (4) a boy of five years with an indefinite rheumatic history, an

apical systolic murmur, and a globular shaped heart in the roentgenogram; (5) a girl of thirteen years who had had chorea and now presented the evidence of rheumatic heart disease. Patient (1) above, showed a long, flat, low, notched T-wave in Lead IV.

Inasmuch as several of our control tracings showed inverted T-waves of low amplitude (less than 1 mm.) we considered the same finding in our group with cardiac disease to be without significance. There were two cases in which all four leads had T-waves of low amplitude. Otherwise there was no correlation between a low T-wave in Lead IV and low T-waves in the other leads. It is not possible categorically to set the limits of the normal T-wave amplitude—nevertheless, the amplitude of the T-wave in our control group was never less than $\frac{1}{2}$ mm., whereas in those two cases with low amplitude of the T in all leads, T-IV was only $\frac{1}{4}$ mm. in height.

We found T-IV diphasic ten times; in three of these, the two phases were of equal amplitude; in six others, the negative phase was the larger, and in one, the reverse was true. One of our normals displayed a diphasic T-IV of low voltage (Fig. 1) with the positive phase first. It is possible, that to have significance, a diphasic T-IV must have an amplitude of more than 2 mm., particularly when the major portion of the T-wave is upward. The presence of a diphasic T-IV could not be correlated with any particular feature in the other leads; although there was one case in which the T-wave of all four leads was diphasic. The significance of a diphasic T-IV is uncertain.

We found a deep T-wave in Lead IV four times. Twice there was electrocardiographic evidence of myocardial damage. A negative T-wave, 9 mm. or more in depth, therefore should be viewed with suspicion.

Tentatively, in view of our comparatively small series, we are able to state that the following are abnormal T-waves: (1) a positive T-wave, (2) a diphasic T-wave more than 2 mm. in amplitude and with the positive phase the larger, (3) a shallow, broad negative T-wave with an amplitude of $\frac{1}{4}$ mm. or less, (4) a deep negative T-wave with an amplitude of 9 mm. or more. Such T-waves in Lead IV are to be considered suggestive of the presence of myocardial damage. They are naturally less significant when they occur alone than when accompanied by other evidence pointing in the same direction.

S-T Segment.—In eight cases there was a positive S-T deviation in Lead IV, a finding not seen in any of the control tracings. Therefore, a deviation of even a half millimeter above the isoelectric line should be viewed with suspicion. Four of the eight tracings showed a positive deviation of 1 mm. or more, and it was precisely these four tracings that were associated with negative or positive deviations of S-T segments of similar magnitude in the conventional leads. The four tracings with positive S-T segments of less than 1 mm. were not accompanied by S-T deviations in the conventional leads.

Two cases presented a negative S-T deviation which we considered significant. In both the deviation was only 1.5 mm. but was associated with a positive T-wave. The three-lead electrocardiogram showed no S-T deviation. Both patients presented marked clinical and electrocardiographic evidence of myocardial disease. Other instances of negative S-T in Lead IV were found, but in no case was the deviation more than 2 mm., and in all the T-wave was negative.

A positive S-T deviation in Lead IV is abnormal when it is more than 0.5 mm. A negative S-T deviation associated with a negative T-wave should exceed 2 mm. to be beyond the normal, and this we have not seen in this group. A smaller negative S-T deviation is abnormal only when the T-wave is positive.

LEAD IV IN RECENT CORONARY OCCLUSION

During the course of this study, we recorded Lead IV in 11 cases of recent coronary occlusion. The 11 sets of tracings fell into three groups: (1) those with changes characteristic of coronary occlusion in Lead IV, (2) those with an abnormal configuration of Lead IV of the type seen in other kinds of heart disease and therefore not specific for coronary occlusion; and (3) those with Lead IV within normal limits. In any one series of records Lead IV might change from the characteristic type of electrocardiogram to the nonspecific abnormal configuration or to normal.

Three types of specific changes were seen. The first, and most common, consisted of a positive S-T segment followed by a negative coronary T-wave which differed little from the normal T-wave. In succeeding records the S-T segment became isoelectric and the T-wave became deeper and then shallower (Fig. 2). The second, seen twice, was the inverted image of the first, consisting of a negative S-T segment followed by positive coronary T-wave such as was recently described in the three-lead electrocardiogram of Bohning and Katz (Figs. 4A and 4B). The progression of this type was similar to that of the first. The third type, seen three times, was a diphasic T-wave of large magnitude, the first phase of which merged with the descending and sometimes entirely negative S-T segment. The transition between the negative and positive phase was abrupt, making the positive phase sharply peaked (Figs. 3A and 3C).

In two instances Lead IV of low amplitude was associated with low amplitude of the other leads and minor deviations of the S-T segment in all leads (Fig. 3B). This type of tracing, if succeeding records show even slight changes, would tend to substantiate the clinical diagnosis of recent coronary occlusion.

On comparing Lead IV with the three-lead electrocardiogram we found tracings: (1) in which the characteristic changes occurred in all four leads (Figs. 2, 3A and 3B), (2) in which the characteristic changes occurred only in the three standard leads, and (3) in which the characteristic

changes occurred only in Lead IV (Figs. 3C, 4A, 4B and 4C). It is because of this last group that *Lead IV should be taken routinely in all cases of suspected recent coronary occlusion*. This is the plan now followed at the Michael Reese Hospital.

Lead IV varied in appearance in successive tracings when serial records were taken. This is shown in the illustrations. Both the negative and positive coronary T-waves passed through the classical series of changes (Figs.

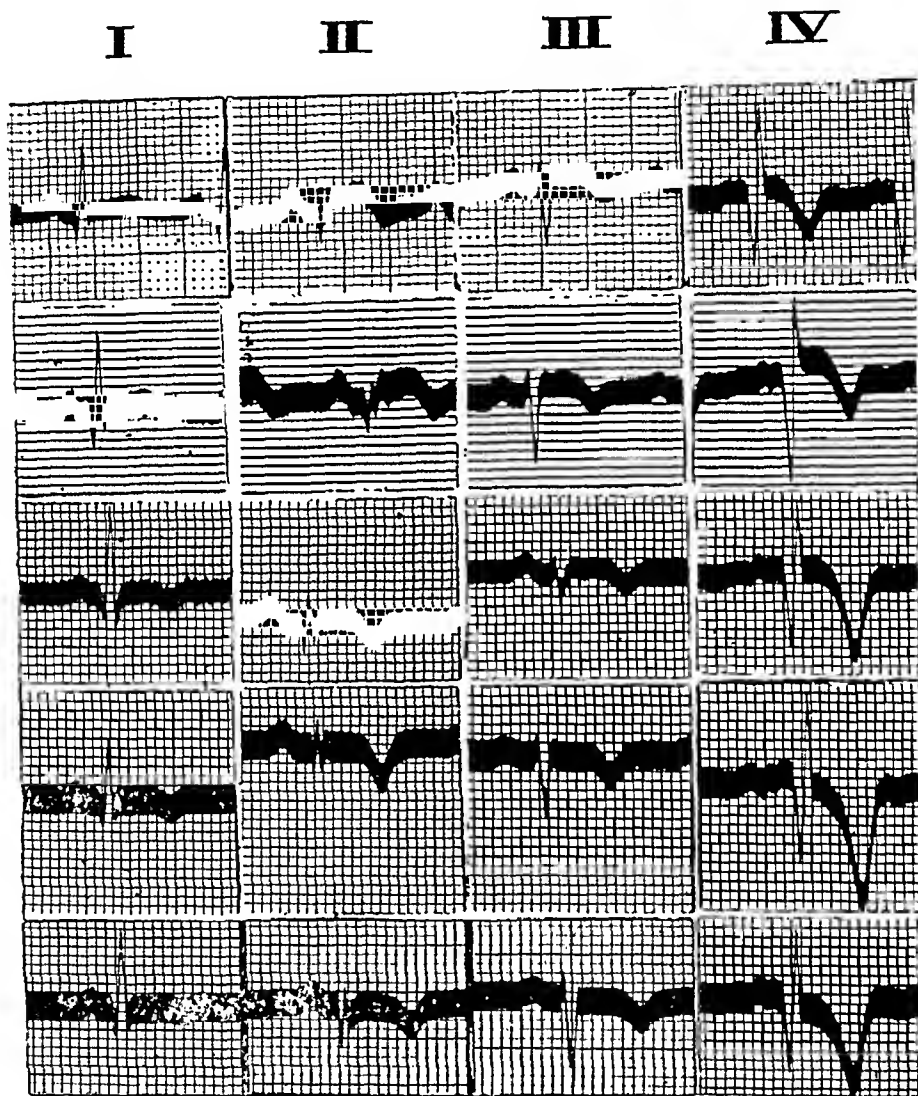


Fig. 2.—Serial electrocardiograms from a case of coronary occlusion. Note the S-T deviation in Leads II, III and IV. The T-wave passes through characteristic changes in all leads.

2, 4B, and 4C) ; although in one case, with almost monophasic ventricular deflections in the standard leads, the negative T-wave became diphasic in a later record, and the positive S-T segment became negative (Fig. 3A). In one case a diphasic T-wave became negative in a later record (Fig. 3C). Quite frequently Lead IV appeared normal at one stage. In several instances QRS became monophasic and positive.

The progression of the changes in Lead IV did not always parallel those in the ordinary leads. Sometimes Lead IV changed less rapidly than the other leads, but usually the reverse was true. Occasionally all leads progressed in parallel fashion.

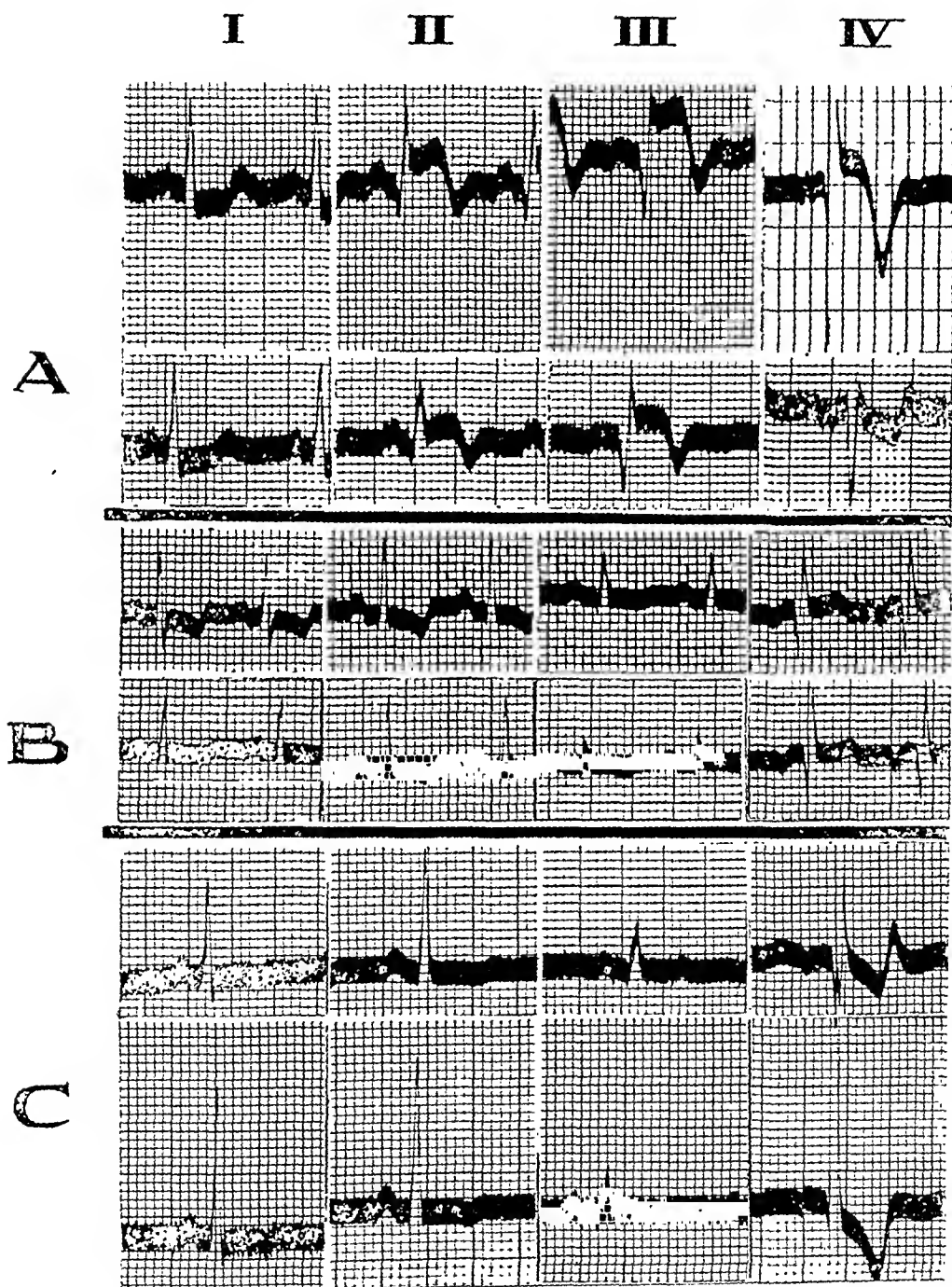


Fig. 3.—Serial electrocardiograms from three cases of coronary occlusion. Note in *A* and *B* changes in all four leads; in *C* changes only in Lead IV. Note in *B* low "voltage" in all four leads.

While it is true that Lead IV helps to explore the heart currents more thoroughly and that with it fewer cases of coronary occlusion will be missed

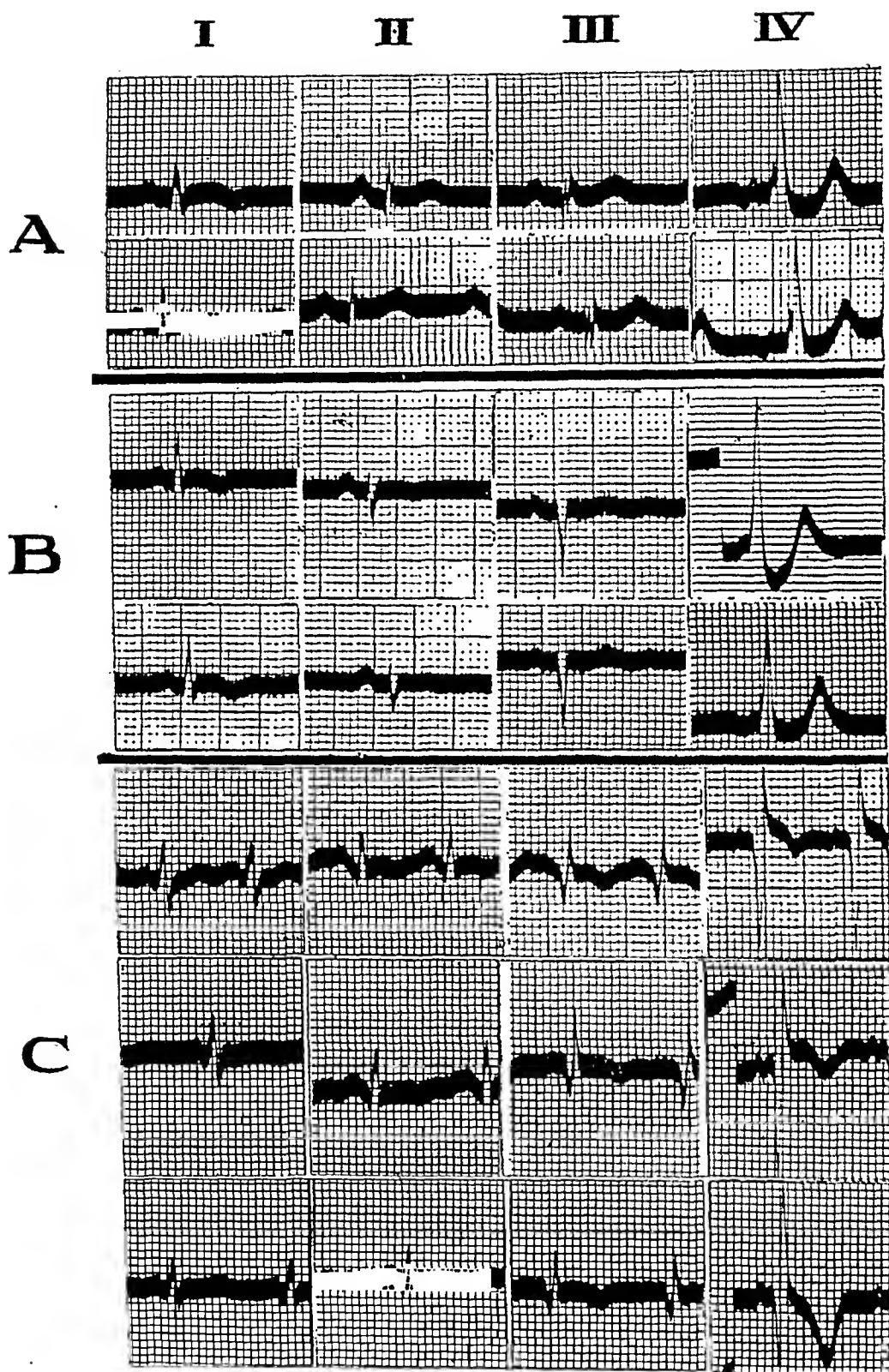


Fig. 4.—Serial electrocardiograms from three cases of coronary occlusion showing characteristic changes only in Lead IV. Contrast the large amplitude of the QRS complex in Lead IV of A with the low amplitude of the QRS complex in Lead IV of Fig. 3B, although the three-lead electrocardiogram in both instances is of low amplitude.

with the electrocardiogram, it is too early to hope that this lead will aid in the localization of the site of infarction, as Wolferth and Wood¹ anticipated.

SUMMARY

1. Lead IV (Wolferth and Wood¹) normally has an inverted or diphasic P-wave, a diphasic QRS, the first phase of which is inverted, and an inverted T-wave resembling superficially the negative coronary T-wave. The characteristics and limits of normal in our 25 cases are discussed in detail.

2. The time relationships of the deflections of Lead IV are the same as those in the other leads.

3. Lead IV can separate those cases in which low amplitude in the three-lead electrocardiogram is caused by change in the heart's position from those due to intraventricular block or increased body shunting.

4. Noticeable slurring and notching of QRS in Lead IV is to be regarded as abnormal and should be considered in the same light as slurring or notching in Leads I or II. There is no constant change in Lead IV in left axis deviation shift or left ventricular preponderance. A monophasic QRS in Lead IV indicates myocardial damage.

5. The following are abnormal T-waves in Lead IV and suggest myocardial damage: (a) a positive T-wave, (b) a diphasic T-wave, taller than 2 mm. and with the positive phase the larger, (c) a shallow broad negative T-wave less than $\frac{1}{4}$ mm. high, (d) a negative T-wave deeper than 9 mm.

6. A positive S-T segment, a negative S-T segment of more than 2 mm., or any negative S-T deviation when associated with a positive T-wave are indicative of myocardial involvement.

7. The presence of any one of the abnormalities in Lead IV described above are to be considered in the same way as abnormalities of the QRS complex, S-T segment and T-wave of the ordinary leads. They are less significant when they occur alone than when accompanied by other electrocardiographic evidence pointing in the same direction.

8. Three types of changes occurring in Lead IV are "specific" for recent coronary occlusion: (a) a positive "humped" S-T segment with a negative coronary T-wave, (b) a negative "humped" S-T segment with a positive coronary T-wave, (c) a diphasic coronary T-wave which is transient. The first two types pass through the usual sequence in a series of records described for other leads. The progression of changes in Lead IV in a series of records is not always parallel to that in the ordinary leads. Often the changes progress most rapidly in Lead IV.

9. While Lead IV may show no abnormalities, or only nonspecific types of abnormalities in recent coronary occlusion, there are in the five cases reported by Wolferth and Wood^{1, 2} and the 11 reported by us, a sufficient

number of cases (7 out of 16) in which the specific changes occurred only in Lead IV. *Therefore, Lead IV should be taken routinely in all cases of suspected recent coronary occlusion.*

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THE ETIOLOGY OF HEART DISEASE IN WHITES AND NEGROES IN TENNESSEE*

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THE diagnosis of "heart disease" does not convey an idea of the nature of the disease process, because the underlying etiology varies and is sometimes multiple. Obviously, the first step in the development of a program of prevention of heart disease is the acquirement of knowledge of the etiological factors involved. These factors have been found to vary with the geographical location, race, climate, and mode of life.

Studies of large groups of patients with heart disease from the point of view of etiology have been reported in this country by White and Jones,⁶ Wood, Jones, and Kimbrough,⁸ Davison and Thoroughman,² Coffen,¹ Stone and Vanzant,⁴ Viko,⁵ Schwab and Schulze,³ and others. Such studies have a twofold value; they add to the accumulated data concerning the etiology of heart disease, and they also enable local groups to visualize their particular problems. The study reported here was initiated with these two objectives.

The patients studied were those admitted to the wards and out-patient department of the Vanderbilt University Hospital during the calendar years 1930 and 1931. This group includes both whites and negroes and represents diverse economic levels. A study of such a series, therefore, not only affords information concerning the incidence and etiology of heart disease in the general population of Tennessee but also offers an opportunity to compare these findings in the white and negro races.

During the two-year period 16,935 new patients were admitted to the various divisions of the out-patient department and the hospital. Of this number 11,198 (66.2 per cent) were whites and 5,737 (33.8 per cent) were negroes. This ratio closely approximates the racial percentages in the vicinity of Nashville. From these patients were selected all those who exhibited definite objective evidence of heart disease. These numbered 645, and each of them showed one or more of the following evidences of cardiac disease: unequivocal cardiac enlargement, congestive heart failure, mitral stenosis, aortic insufficiency and/or stenosis, congenital abnormality, auricular fibrillation, auricular flutter, heart-block (electrocardiographic evidence), coronary occlusion, angina

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pectoris, pericarditis (acute or chronic), bacterial endocarditis, aneurysm of the aorta.

The records of these 645 cases were then subjected to analysis. Each record included a history, a physical examination, and the results of Wassermann test, urinalysis, and other indicated laboratory procedures. Cardiac measurements were verified by teleroentgenogram in 434 (67.4 per cent) and electrocardiographic tracings made in 362 (56.2 per cent) of the patients. One hundred and sixteen of these 645 died during the two-year period and 71 autopsies were obtained. In only one case was the pre-mortem diagnosis of *etiology* altered by the post-mortem examination. On the basis of all available information each patient was classified etiologically, or placed in the "unclassified" group if adequate evidence was lacking. The classification used and the criteria for the classification are the ones proposed by White and Myers,⁷ with certain modifications, which consist mainly of a consolidation of the hypertensive and arteriosclerotic groups of heart disease. We found it impossible to separate these groups of cases with any degree of accuracy. A large percentage of these who showed definite arteriosclerosis had hypertension, and some of those with arteriosclerosis and cardiac hypertrophy who did not have an elevated blood pressure when observed may well have had it in the past. In each instance of mixed etiology, if there was not an etiological factor which was clearly dominant, the case was grouped with those of doubtful or unknown etiology under the heading "Unclassified." The number so placed was small and does not serve to alter appreciably the percentages in the other groups.

RESULTS

I. Incidence.—Table I reflects the incidence of organic heart disease among the 16,935 patients admitted. The total incidence of 3.8 per cent is of less significance than the difference in the incidence in the two race groups. Four and nine-tenths per cent of the negroes seen but only 3.3 per cent of the whites had heart disease.

TABLE I
INCIDENCE OF ORGANIC HEART DISEASE IN 16,935 PATIENTS

Patients Admitted to Wards and Out-Patient Department		Percentage of total
White	11,198	66.2
Negro	5,737	33.8
Total	16,935	100.0
Organic Heart Disease Among the Group		Percentage of racial group
White	365	3.3
Negro	280	4.9
Total	645	3.8

II. Occurrence of Etiological Types.—In Table II are summarized the etiological factors in our 645 cases of heart disease and their relation to age groups and race. In general these data indicate that arteriosclerotic-hypertensive disease (67.9 per cent), the rheumatic fever complex (10.5 per cent), and syphilis (7.9 per cent), together cause 86.3 per cent of the heart disease observed in the Vanderbilt University Hospital. They also emphasize that while heart disease due to arteriosclerosis and hypertension occurs with almost equal frequency in the white and negro races, rheumatic heart disease assumes a frequency in the white race similar to the frequency of syphilitic heart disease in the negro. This last point is borne out by the figures collected (in Table III) from various clinics having the opportunity to compare large groups of white and negro patients.

a. *Arteriosclerotic-Hypertensive Heart Disease.* This group includes 438 patients (67.9 per cent of the series). It is thus numerically much the most important group. This type of heart disease affects 71.8 per cent of the negro patients and 65.1 per cent of the white. The most constant physical finding in this group is cardiac hypertrophy, which was present in 95.9 per cent of our cases. In 59.2 per cent of the 438 patients, teleroentgenograms were made. Electrocardiograms in 226 cases revealed auricular fibrillation in 28 (6.4 per cent of the group), bundle-branch block in 15 (3.4 per cent), and signs usually ascribed to coronary occlusion in 5 (1.1 per cent). All the 19 cases of angina pectoris which were seen during the period under review had definite evidence of arteriosclerotic-hypertensive heart disease, and have been included under this classification. Although 201 negroes are in this etiological group, only 3 of them had angina pectoris. Ninety-six (21.9 per cent) of the patients in this group were at least 20 per cent overweight.

b. *Rheumatic Heart Disease.* This group of 68 patients (10.5 per cent of the series) includes 15.3 per cent of the cases of heart disease in the white race and only 4.3 per cent of the cases in the negroes. The valves involved were as follows:

Mitral alone	44
Aortic alone	3
Mitral and aortic	21

In no instance was the diagnosis of adhesive pericarditis made. Electrocardiograms of 52 of the cases revealed: auricular fibrillation in eight instances, varying degrees of heart-block in three, and nodal rhythm in two.

c. *Syphilitic Heart Disease.* Of the 51 patients (7.9 per cent of the series) who had syphilitic heart disease, 43 were negroes. This type of heart disease accounted for 15.4 per cent of the negro cases, exactly seven times the frequency with which it was encountered in whites

TABLE II
ANALYSIS OF 645 CASES OF ORGANIC HEART DISEASE

ETIOLOGY		AGE GROUPS								80+	MALE	FEMALE	TOTAL	PERCENTAGE	
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79					RACIAL OF TOTAL	65.1
Arteriosclerosis and hypertension	White	1	1	3	10	36	71	69	39	7	148	89	237	65.1	
	Negro			5	27	46	70	40	12	1	89	112	201	71.8	
	Total	1	1	8	37	82	141	109	51	8	237	201	438		67.9
Rheumatic infection	White	4	18	17	11	4	2				23	33	56	15.3	
	Negro		1	6	4		1				6	6	12	4.3	
	Total	4	19	23	15	4	3				29	39	68		10.5
Syphilis	White				2	2	3	1			6	2	8	2.2	
	Negro				14	12	13	2			37	6	43	15.4	
	Total				16	14	16	3			43	8	51		7.9
Congenital defect	White	7	3	4	2		1				10	5	15	4.1	
	Negro	1	3	2							5	1	6	2.1	
	Total	8	6	6							15	6	21		3.3
Bacterial endocarditis	White		1	1	3		1	3			6	4	10	2.7	
	Negro						2				1		1	0.4	
	Total										7		11		1.7
Diphtheria	White	8		2	1		1	3			4	4	8	2.2	
	Negro						2				1	3	4	1.1	
	Total						3				5	7	12		1.2
Thyrototoxicosis	White					1	1							1.1	
	Negro						2				1	6	7		1.1
	Total						3				2	6	9		1.1
Chronic pulmonary disease	White					1		1			2	1	3	0.8	
	Negro					1					2	2	3	0.7	
	Total					2		1			4	3	7		
Trauma	White			2		3		1			2	1	5	0.8	
	Negro													0.7	
	Total														
Miscellaneous infections	White	1	1	1	1	3	2	1			2	2	10	2.7	
	Negro						1				3	1	4	1.4	
	Total	1	1	1	1	3	3	1			5	3	14		2.2
Unclassified	White					2					11	6	17	3.8	
	Negro					5	1	2			8	4	12	2.1	
	Total					7	2	2			19	10	29		3.1
Total	White	22	26	32	29	50	83	77	39	7	216	149	365	100.0	
	Negro	1	4	20	50	62	88	42	12	1	149	131	280	100.0	
	Total	23	30	52	79	112	171	119	51	8	365	280	645		100.0

TABLE III
COMPARATIVE STATISTICS ON THE ETIOLOGY OF HEART DISEASE IN THE SOUTH

NO. OF PATIENTS	TEXAS ⁴		GEORGIA ²		VIRGINIA ⁵		TEXAS ³		TENNESSEE*		TOTAL	
	WHITE	NEGRO	WHITE	NEGRO	WHITE	NEGRO	WHITE	NEGRO	WHITE	NEGRO	WHITE	NEGRO
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Arteriosclerotic and hypertensive	65.0	56.8	61.3	59.0	60.7	60.7	73.3	76.8	65.1	71.8	66.9	65.6
Rheumatic	10.4	3.6	7.2	28.3	11.6	11.6	7.4	1.8	15.3	4.3	15.4	5.7
Syphilitic	9.2	31.7	25.3	4.7	21.4	—	6.8	15.3	2.2	15.4	5.8	21.8
Congenital	1.0	0.2	0.8	1.5	—	—	0.6	0.8	4.1	2.1	1.8	0.8
Thyrototoxic	1.4	1.2	—	3.9	3.6	—	2.9	2.3	1.1	1.1	2.4	1.6
Subacute bacterial en- docarditis	—	—	—	—	—	—	—	—	—	—	—	—
Miscellaneous	1.8	1.2	1.2	—	—	—	—	—	2.7	0.4	1.1	0.5
Unclassified	1.4	1.2	—	2.1	2.7	—	2.5	2.3	2.7	1.4	2.0	0.9
Angina pectoris	5.6	4.1	4.2	—	—	—	—	—	3.8	2.1	3.5	3.1
	4.2	—	—	—	—	—	—	—	—	—	1.1	—

*Present report.

(2.2 per cent). The marked preponderance of syphilitic heart disease in males of both races bears out previous studies.^{2, 3, 4, 6, 8} The cardiac lesions were as follows:

Aortic insufficiency	30	58.8 per cent
Aortic insufficiency and aneurysm	10	19.6 per cent
Aneurysm alone	8	15.7 per cent
Myocardial lesions	3	5.9 per cent

Electrocardiograms in thirty cases revealed two with bundle-branch block.

The presence of arteriosclerosis and systolic hypertension among this group was a frequent finding as shown below:

Hypertension and arteriosclerosis	21
Hypertension without manifest arteriosclerosis	11
Arteriosclerosis without hypertension	3
No hypertension or arteriosclerosis	16
	<hr/> 51

A systolic hypertension was observed in thirty-two of the fifty-one patients in this group, but in only eight of these thirty-two cases with hypertension was the diastolic pressure above 90. These eight undoubtedly represent a mixed type of etiology with the hypertension playing a rôle in the disability, but from careful study of the patients the principal cardiac damage can be attributed to the luetic infection.

Substernal pain was a frequent symptom in the patients of this group, but not one of them gave a history typical of angina pectoris.

d. Miscellaneous Types of Heart Disease. The remaining types of heart disease were so limited in number as to furnish little of statistical interest, aside from their ratio to the total number of cases of heart disease.

III. Racial Comparison.—The data in Table III, a summary of 2,235 cases of heart disease in the negro and 1,542 cases in the white race, are all drawn from published statistics collected in southern hospitals and dispensaries. The first group was compiled by Stone and Vanzant from patients seen in Galveston, Texas; the second by Davison and Thoroughman in Atlanta, Georgia; the third by Wood et al. in Richmond, Virginia; the fourth by Schwab and Schulze in Galveston, Texas; the fifth is our series. The criteria for diagnosis were essentially the same in all.

It is at once apparent that in the negro race the two main causes of heart disease are arteriosclerosis-hypertension and syphilis. Both of these processes are primarily vascular, so that it appears reasonable to suppose that the vascular system of the negro is susceptible to attack by disease processes.

In addition to the differences in the incidence of etiological factors in the two races, the negro develops heart disease at an earlier age,

on the average, than the white. Fig. 1 shows graphically the abrupt rise in the incidence of arteriosclerotic hypertensive heart disease in successive age groups in the negro race as compared with the more gradual ascent and decline in the white race. Stone and Vanzant⁴ have prepared a similar chart in their study, and the difference is even more striking. Likewise, in the incidence of syphilitic heart disease, the negro race shows a tendency to reach a peak at least a decade before the white race. It is true that the number of white patients with syphilitic heart disease in our series is too small to furnish comparable statistics, but analyses by White and Jones⁶ and Viko⁵ of syphilitic heart disease in their communities furnish figures which may be compared with our studies of the negro, and bear out this contention.

Angina pectoris is rare in our negro patients. Substernal pain is not an uncommon complaint with them, but the typical attacks of paroxysmal pain so characteristic of angina pectoris are seldom found.

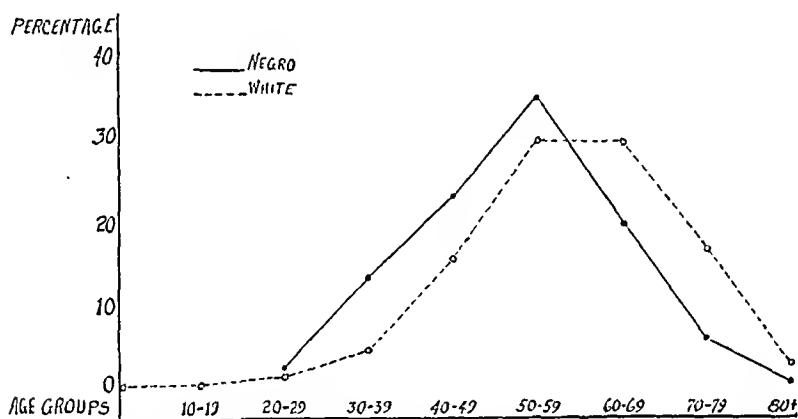


Fig. 1.—Arteriosclerotic hypertensive heart disease, age incidence.

Rheumatic fever, subacute bacterial endocarditis, and miscellaneous infectious processes are much less common causes of heart disease in the negro. The statistics furnished in Table III indicate that such types of heart disease are at least two or three times as common in the white race.

It is apparent that heart disease in the South differs somewhat in etiology from heart disease in other parts of the United States. The large negro population, with its increased incidence of syphilitic heart disease, and the comparative infrequency of the rheumatic infection make our approach to the preventive program somewhat different from that advisable in other sections. The greatest single cause, arteriosclerosis-hypertension, remains, however, as a universal problem.

SUMMARY AND CONCLUSIONS

1. Six hundred forty-five cases of organic heart disease were studied with reference to etiology, racial distribution, sex, and age.

2. Organic heart disease occurred in 4.9 per cent of all negroes coming to the Vanderbilt University Hospital and Out-Patient Department in 1930 and 1931, and in 3.3 per cent of the whites. The incidence in the negro race was therefore 1.5 times greater than in the white race.

3. Arteriosclerotic hypertensive heart disease accounted for 65.1 per cent of the cases in the white race and 71.8 per cent in the negro race. Rheumatic heart disease formed 15.3 per cent of the cases in the whites and only 4.3 per cent in the negroes, while syphilitic heart disease was seven times more common in the negro than in the white, 15.4 per cent and 2.2 per cent respectively.

4. Comparative statistics from various sources show that the etiology of heart disease varies somewhat in different sections of the United States. Therefore, the problems of the prevention of heart disease are not identical in all parts of the United States.

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THE SILHOUETTE OF THE HEART AND THE AORTIC ARCH

ORTHODIAGRAPHIC MEASUREMENTS

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TRANSVERSE DIAMETER

TO ESTIMATE the size of the human heart various measurements have been suggested; principally, the transverse diameter of the frontal plane at its widest points, the combination of different diameters and the surface area of the frontal plane. The transverse diameter is the measurement most commonly employed. It is practicable because it can be obtained in a few seconds, requiring only ordinary care and no special skill. It can be accurately measured only by orthodiagraphy.

The validity of the transverse diameter as an index of the heart's size is attested by the work of Bardcen,¹ of Hodges and Eyster,² of Bedford and Treadgold,³ of Treadgold and Burton,⁴ and by my own work.⁵

Standards.—Inasmuch as normal hearts vary considerably in size, such a measurement will have value if it can be established that it is not haphazard, but that it bears a constant relation to some standard which is adjustable to normal variations of size. Several standards, all based on the physical characteristics of human beings, have been proposed for estimating or predicting what the transverse diameter of the heart should be in any normal individual.

In a previous paper⁵ the accuracy of Hodges and Eyster's prediction formula² and that of cardiothoracic ratio⁷ were tested by comparing the actual diameters obtained by orthodiagrams with the estimated normal diameters in 100 "noncardiac" males and 75 "noncardiac" females. For females an adjusted standard which is 0.8 cm. smaller than the male prediction figure was used.

Standards based on weight, on body surface area and on height are now added. To obtain the weight standard the subjects were arranged in groups, each group comprising individuals weighing within 5 kilograms of each other. The average transverse diameter for a group was used as a standard, and the difference between this figure and the actual transverse diameter of each individual heart in the group was considered the variation from the standard or predicted diameter for that case. This is the method used by Treadgold and his associates.^{3, 4} To obtain the body surface area standard, a similar plan used by

Kissane⁶ was adopted, taking 0.1 square meter as the range of measurement for each group. Individuals within 2.0 cm. of each other formed the groups for getting the height standard.

Table I presents the comparative merits of each prediction method by showing the percentage of cases whose actual transverse measurements are within 0.5 cm. of the predicted diameter, of those within 1.0 cm., and also the percentage of those that are wider by more than 1.0 cm. In the last column the average variation of the actual from the predicted diameter is recorded. The 100 normal male hearts are used in making the comparison.

TABLE I
THE ACTUAL TRANSVERSE DIAMETER

	WITHIN \pm 0.5 CM. OF THE PREDICTED DIAMETER PER CENT	WITHIN \pm 1.0 CM. OF THE PREDICTED DIAMETER PER CENT	LARGER BY MORE THAN 1.0 CM. PER CENT	AVERAGE VARIATION CM.
Hodges and Eyster formula	61	85	6	0.53
Weight	51	86	10	0.61
Body surface area	47	72	13	0.73
Height	34	61	20	0.94
Cardiothoracic ratio	28	60	17	1.00

The figures in this table indicate that while the formula of Hodges and Eyster is not perfect, it is a better criterion than any of the others. According to the average variations found it is superior to the weight standard by 15 per cent, to the standard based on body surface area by 37 per cent, to the height standard by 77 per cent and to the cardiothoracic ratio by 90 per cent. Treadgold and his associates acknowledge the superiority of Hodges and Eyster's formula, but consider the weight standard as used by them a satisfactory guide for clinical purposes. They seek to improve the weight standard by adding to the estimated transverse diameter when the weight of an individual is above the average for his physique and by subtracting from it when the height is above the average. This is the fundamental principle of Hodges and Eyster's formula wherein the predicted diameter is directly proportionate to weight and inversely proportionate to height. My own data on the actual diameter in both male and female hearts are generally in accord with this principle.

If the transverse diameter of a normal heart is directly proportionate to weight and inversely proportionate to height, then it follows that a prediction figure based on body surface area is untenable as a standard because body surface area is directly proportionate to both height and weight. The comparative figures in Table I substantiate this conclusion.

It is rather surprising that the cardiothoracic ratio which has been so universally employed as a guide in judging the size of the heart should prove to be the poorest standard of all those considered.

Enlargement.—Hodges and Eyster concluded that the chances are three to one in favor of pathological increase in size of the heart when the transverse diameter is wider than the predicted diameter by more than 0.5 cm. Eyster evidently considered such a limitation of the normal too narrow, for he later⁸ expressed the opinion that a heart was enlarged when its transverse diameter exceeded the predicted diameter by more than 10 per cent. This conclusion apparently is based on data from two series, each 100 normal cases, in the first⁹ of which only three hearts exceeded this measurement and in the second⁸ only eight hearts. In only 5.5 per cent of 200 normal cases, therefore, did the transverse diameter exceed the predicted diameter by more than 10 per cent. Bedford and Treadgold³ submitting a group of 116 normal cases to Hodges and Eyster's formula found only 4.3 per cent with an increase of more than 10 per cent.

In my own series of 175 cases⁵ the actual increase in size instead of the percentage was used. Seven cases or 4 per cent had a transverse diameter wider than the predicted diameter by more than 1.0 cm. There is no difference between 1.0 cm. increase and 10 per cent increase in a heart whose transverse diameter is 10.0 cm., and in a heart of average size the difference is too small to be of any practical importance in ordinary clinical work.

As a result of these separate orthodiagraphic studies on the transverse diameter of 491 normal hearts, one is in a position to establish a line of demarcation between normal and enlarged hearts. Twenty-three hearts, or a little less than 5 per cent, had a transverse diameter either 10 per cent or 1.0 cm. wider than the predicted diameter, and it is therefore fair to conclude that when a heart is found with this degree of increased size the chances are over 95 per cent in favor of such a heart being pathologically enlarged.

As a definition of enlargement this criterion applies only to hearts previously normal in size, because an abnormally small heart may increase considerably in volume before its transverse diameter is 1.0 cm. larger than the predicted figure.

Table II presents an arrangement showing the variation of the actual transverse diameter from the predicted diameter according to formula of Hodges and Eyster in 175 normal individuals contrasted with 471 abnormal cases, the latter being divided as follows: 44 with functional disturbance but with no evidence of structural change, 70 in whom the diagnosis was uncertain and therefore called possible heart disease¹⁰ and 357 with organic heart disease.

The measurements of 84 cases of the total 646 have been omitted from the table because the transverse diameter was smaller than the predicted diameter by more than 0.5 cm. They are divided as follows: normal 41, noncardiac with functional disturbance 8, possible heart disease 12, and pathological group 23. All subjects were ambulatory.

TABLE II
THE ACTUAL TRANSVERSE DIAMETER

	CASES	WITHIN ± 0.5 CM. OF PREDICTED DIAMETER		WIDER THAN PRE- DICTED DIAMETER BY MORE THAN 0.5 CM. BUT LESS THAN 1.0 CM.		WIDER THAN THE PREDICTED DIAMETER BY MORE THAN 1.0 CM.	
		CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Normal	175	106	60.5	21	12	7	4
Noncardiac with func- tion disturbance	44	28	63.5	6	13.6	8	4.5
Possible heart disease	70	27	38.5	15	21	16	23
Pathological	357						
1. Thyrotoxic	11	5	45	2	18	3	27
2. Hypothyroid	2	0	0	0	0	2	100
3. Cardiac insuffi- ciency	12	1	8	1	8	9	75
4. Mitral stenosis	39	11	28	11	28	14	36
5. Mitral stenosis and insufficiency	29	4	14	0	0	24	83
6. Mitral insuffi- ciency	27	6	22	4	15	16	54
7. Mitral and aortic disease	34	1	3	2	6	31	91
8. Luetic Aortitis	9	1	11	2	22	6	66
9. Coronary sclerosis without hyperten- sion	51	17	33	9	1.7	17	33
10. Coronary sclerosis with hypertension	45	17	38	4	9	24	53
11. Sclerosis of aorta with hypertension	33	2	6	5	15	24	73
12. Sclerosis of aorta without hyperten- sion	13	4	30	2	15	6	46
13. Essential hyperten- sion	52	14	27	10	20	23	44
Total Pathological group		83	23	52	14	199	56

It is generally recognized that heart disease does not always cause manifest enlargement of the heart. Table II indicates that this is frequently so, 27 to 45 per cent in such conditions as thyrotoxicosis, mitral stenosis, coronary sclerosis, both with and without hypertension, and essential hypertension. There are certain factors, however, which must be considered in the interpretation of these figures. In many of the pathological cases the absence of increased size may be more apparent than real. For purposes of this study hypertension was considered present when the blood pressure was over 140/90 mm.,¹² or when the systolic pressure was over 150 mm. regardless of the diastolic pressure,

or the diastolic pressure over 100 mm. regardless of the systolic pressure. Using this criterion no cases of hypertension could escape detection, but at the same time some patients, seen but once, may have had only a temporary rise of pressure due to the excitement of the examination. It is possible that this condition may account partly for the normal range in size in some cases of hypertension.

It is also possible that a few of these pathological hearts may have been unduly small before the advent of disease and as a result of disease may have increased considerably in size and still be included within the confines of the normal or borderline measurements. For example, a heart which in health was 1.0 cm. smaller than the normal range would have to increase its transverse diameter by more than 2 cm. before it could be included in the group of large hearts. Fortunately changes in contour often will indicate that there is enlargement of the heart or of some of its chambers regardless of the actual measurements. However, this study has been concerned not with enlargement as such, but only with the significance of size in hearts whose transverse diameter is larger than the predicted by more than 1.0 cm.

With these reservations in mind it is reasonable to expect that in any mixed group of pathological cases 56 per cent of the hearts will be found enlarged as against 4 per cent of the normal cases, while 44 per cent will not show that increased size as against 96 per cent of normals. The 44 noncardiac patients with functional disturbances, but with no evidence of structural disease, have hearts with approximately the same measurements as normal individuals, an agreement which is consistent with the diagnosis. In Class E (possible heart disease) 23 per cent of hearts are in the large group, as against 4 per cent of normal hearts and 56 per cent of pathological hearts, indicating some justification for the unsatisfactory designation of possible heart disease.

WIDTH OF AORTIC ARCH

The frontal plane of the so-called base of the heart forms a shadow under the x-ray which includes the ascending aorta and arch, the pulmonary artery and at times the first part of the descending aorta. The outline is usually delineated with ease in an orthodiagram from which exact measurements can be made. Such measurements have a limited value, but may be useful in providing information about the variations in size in that part of the silhouette which is produced by the ascending aorta and arch. For this purpose one of three different measurements has been employed.

One measurement near the top of the arch is made from the farthest point on the left of the aortic knob to the farthest point on the right at which the aortic shadow is visible at this level (*b* and *c* in Fig. 2). Aside from the difficulty of visualizing the right border of the aorta at this

level because it is so frequently hidden by the bony shadows of the sternum and vertebral column, this measurement has a doubtful value. It represents the base of a curve formed merely by a segment of the

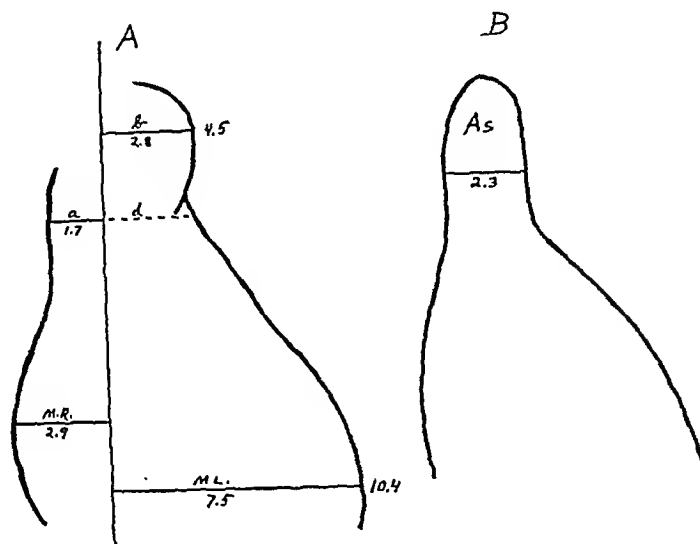


Fig. 1.—Normal female, aged twenty-five years, weight 57 kilo., height 154 cm. A, Orthodiagram, anteroposterior position: TD 10.4 cm., (predicted TD 10.6 cm.); width of aortic arch ($a+b$) 4.5 cm., (average normal width 4.6 cm.); width of great vessels $a+d$.

B, Orthodiagram, right oblique position; diameter of ascending aorta (As) 2.3 cm.

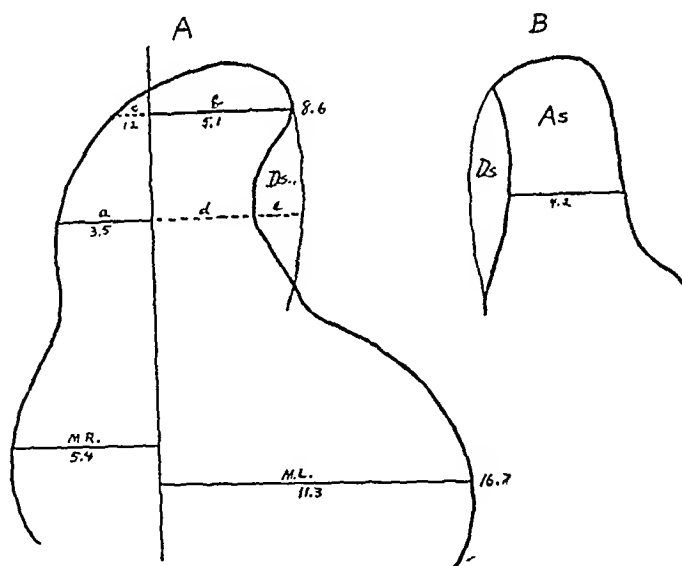


Fig. 2.—Male, aged fifty-five years, weight 84 kilo., height 175 cm. Diagnosis arteriosclerosis and hypertensive heart disease.

A, Orthodiagram, anteroposterior position; TD 16.7 cm. (Predicted TD 13.5.); width of aortic arch ($a+b$) 8.6 cm. (average normal width 6.1 cm.); line of measurement near upper border of arch, $b+c$; width of great vessels $a+d+c$; Ds , descending aorta.

B, Orthodiagram, right oblique position: Diameter of ascending aorta (As) 4.2 cm.; Ds , descending aorta.

arch. If the ascending aorta passes diagonally beneath the sternum, the measurement will be much smaller than if the course of the vessel is more vertical. This is seen in Fig. 2A where there is considerable in-

crease in the width of the shadow produced by the ascending aorta and arch, while the measurement of $b + c$ which is 6.3 cm. would indicate that the size of the silhouette is normal.

A second measurement is called the diameter or width of the great vessels. In Figs. 1A and 2A this is represented by the lines a and d , the shadow being produced by the ascending aorta and pulmonary artery which lie side by side at this point. The shadow cannot be separated into the two component parts, and, if there be increase in size, it is impossible to tell from this measurement whether an abnormality in the aorta or pulmonary artery is responsible for the enlargement. In Fig. 2A the line a , d and e represents the width of the same two vessels in addition to that part of the descending aorta which can be visualized. Lying in a deeper vertical plane the silhouette of the descending aorta is easily identified. It is usually seen only when there is tortuosity or dilatation of the descending aorta, but inasmuch as the complete width of the vessel is never visualized in this position, any measurement of the shadow is quite valueless.

The measurement chosen for this study is that suggested by Vaquez and Bordet¹¹ which they call the transverse diameter of the arch. Measurement is made from the midsternal line to the farthest point on the right of the ascending aorta and to the farthest point on the left of the aortic knob (a and b in Figs. 1 and 2). The sum of these two measurements represents the width of the aortic arch. It is actually the base of an arch formed by the outer margins of the shadows of the ascending aorta and arch.

In making an orthodiagram of the width of the aortic arch care must be exercised to differentiate the ascending aorta from the superior vena cava. The former almost always shows a border which is more or less convex, the latter a border which is straight in the lower part and usually slightly concave in the upper part. Occasionally the ascending aorta is completely hidden by the bony shadows of the sternum and vertebral column.

This measurement of the basal silhouette is not a measurement of any one structure. It is really an index of the size of the curve produced by the shadows of the ascending aorta and arch and has a value only if it can be shown that it is fairly constant in normal individuals and is subject to change in dimensions under the influence of abnormal conditions of the vessel.

Table III presents the measurements obtained from normal individuals.

Table III shows the average width of the aortic arch in 178 adults according to sex and age. The figures of Vaquez and Bordet¹¹ are added for comparison. The table indicates that the shadow has a wider

TABLE III
 WIDTH OF AORTIC ARCH

NORMAL MALES				
AGES	CASES	AVERAGE WIDTH	EXTREMES	VAQUEZ AND BORDET
		CM.		CM.
17-19	9	4.6	4.0 to 5.0	4 to 5
20-29	24	5.2	4.2 to 6.6	5 to 6
30-39	21	5.5	4.3 to 6.4	5.5 to 7
40-49	25	5.7	4.8 to 6.7	6 to 7
50-59	14	6.1	4.7 to 7.0	
	93			
NORMAL FEMALES				
16-19	11	4.3	3.8 to 5.2	
20-29	31	4.6	3.9 to 5.5	
30-39	24	5.0	4.0 to 6.2	
40-49	13	5.1	4.4 to 5.7	
50-59	6	5.6	5.1 to 6.1	
	85			

measurement in men than in women and that its size gradually increases with age.

Table IV shows the number and percentage of these normal cases having a width of the arch within 0.5 cm. of the average measurement and also the number and percentage of those whose measurement exceeded the average by more than 0.5 cm.

 TABLE IV
 VARIATION FROM THE AVERAGE AORTIC ARCH WIDTH

	WITHIN 0.5 CM. OF AVERAGE WIDTH		MORE THAN 0.5 CM. GREATER THAN AVERAGE WIDTH	
	CASES	PER CENT	CASES	PER CENT
Normal males				
93 cases	71	76	11	12
Normal females				
85 cases	67	78	12	14
Total 178	138	77	23	13

According to this table in 77 per cent of these cases the width of the aortic arch was within 0.5 cm. of the average width for each group according to sex and age. In 13 per cent the width of the arch was greater than the average by over 0.5 cm. The remaining 10 per cent were smaller by more than 0.5 cm. and are not tabulated.

It is to be expected that there will be an increase in the width of the arch in a short heavy individual who has a high diaphragm which tends to push both the heart and the aorta upward. Displacement of this kind will cause a wider sweep in the curve of the first part of the aorta and therefore a greater measurement without a necessary change in the caliber of the vessel. Of the 23 cases with the increased width

of more than 0.5 cm. 14 were appreciably overweight and 10 of these were short in stature.

Inasmuch as only 13 per cent of normal subjects show a measurement of the shadow of the aortic arch which exceeds the average for the group according to sex and age by more than 0.5 cm., it seems fair to conclude that 87 per cent of individuals presenting this degree of increase in size have an enlargement of the silhouette which is due to pathological change. If the short thick-set individuals could be excluded, the prediction figure would be improved.

It would be rather premature to suggest that these figures establish a standard. The final value of such data and the validity of the conclusions may be determined by the examination of a larger number of normal controls and by comparison with groups of pathological cases.

An interesting comparison is made with a group of patients having mitral valve disease, a condition in which one does not expect to find any structural change in the aorta. Ninety-five such patients were examined. In 21 cases the measurement could not be made either because the ascending aorta was obscured or because the contour of the left portion of the arch in many cases of mitral disease is such that the farthest point to the left of the arch shadow cannot be determined with exactness. In 74 cases in which the shadow could be measured 55 (74 per cent) had a width within 0.5 cm. of the normal average and 9 (12 per cent) were wider by more than 0.5 cm. In 10 cases the measurement was smaller than the normal average by more than 0.5 cm. These figures are practically the same as in the normal group.

Comparison of the normal with groups of pathological cases in which an enlarged basal shadow is known to occur with fair frequency is shown in Table V.

TABLE V
COMPARISON OF NORMAL AND PATHOLOGICAL CASES

MALES AND FEMALES	WITHIN 0.5 CM. OF AVERAGE WIDTH		GREATER THAN AVER- AGE WIDTH BY MORE THAN 0.5 CM.	
	CASES	PER CENT	CASES	PER CENT
Normal 178 cases	138	77	23	13
Pathological 138 cases	47	34	81	59
Essential hypertension	16	33	29	60
Hypertension and art. sclerotic aorta	4	21	15	79
Coronary sclerosis, no hypertension	19	53	13	36
Luetic aortitis	1	12.5	7	87.5
Hypertension, all causes	27	29	61	65

In 10 pathological and 17 normal subjects the measurement was smaller than the average by more than 0.5 cm.

There is another significant fact not included in Table V. Of the 23 normal cases which are larger by more than 0.5 cm. only two, or a

little over 1 per cent of the total, have an aortic width greater than the average by more than 1.0 cm. Whereas in the pathological group there are 59 cases, or 43 per cent of the total, showing this degree of increase in width.

No attempt has been made to compare the normal and the pathological shadows in subjects over sixty years old, because it seems impossible to decide what degree of arteriosclerosis is consistent with normal health in people of this age. In 26 men at this time of life without evidence of hypertension the average width of the arch shadow was 6.7 cm. with extremes from 5.0 cm. to 6.9 cm. The average width in 23 men with hypertension was 7.2 cm., the extremes being 5.1 cm. and 9.4 cm.

There are four conditions in which the size of the basal silhouette is increased: syphilitic aortitis, aortic insufficiency, arteriosclerosis of the aorta, and hypertension. The structural change responsible for the increase in the shadow is either dilatation or displacement of the aorta or both of these factors combined. Dilatation of the ascending aorta or arch cannot be estimated in the frontal position. An orthodiagram of the ascending aorta in the right oblique position or of the ascending aorta and arch in the left oblique position will enable one to measure the diameter of the vessel. Fig. 1B shows the ascending aorta in the right oblique position in a normal female subject aged twenty-five years. The aortic diameter is 2.3 cm. Fig. 2B is an orthodiagram of a dilated ascending aorta in the right oblique position in a patient fifty-five years of age with arteriosclerotic and hypertensive heart disease, the diameter of the vessel being 4.2 cm. Vaquez and Bordet¹¹ give 2.0 cm. as the normal diameter of the ascending aorta in men at twenty years of age, with a gradual increase to 3.0 cm. in old age. Quain's *Anatomy* gives 2.8 cm. as the diameter of the ascending aorta in adults and states that "the capacity and the thickness of the walls of large arteries increase gradually with advancing years."

Unfortunately the shadow of the aorta in the oblique positions is often too much obscured to be clearly delineated in an orthodiagram. When one has to depend upon the shadow of the frontal plane only, the diagnosis will be based not on the changes in the shadow only, but on the additional evidence obtained from the history and physical examination of the patient.

Arteriosclerosis of the aorta without dilatation of the vessel may cause an increase in the width of the basal shadow in the anteroposterior position because of the fact that the course of the elongated vessel becomes tortuous, compelling the ascending aorta and arch to assume a more sweeping curve similar to that previously described as occurring in stout normal individuals with a high diaphragm. In these cases the left border of the descending aorta is often visualized as a convex curve

below the aortic knob (D_s in Fig. 2A), and the top of the arch usually reaches a higher position.

Data on rheumatic aortic insufficiency have not been included in Table V because the wide excursion of the aorta so frequently seen in this condition makes it difficult to obtain a drawing of the outline during the diastolic phase and in addition leaves one in doubt whether the aorta is actually dilated or only dilatable under the stress of each systolic discharge from the ventricle. It is also possible that in some instances there may be a wide excursion of the vessel itself without any change in its caliber. A similar excursion of the aorta though not so pronounced is occasionally seen in hypertension and rarely in young neurotic individuals without structural disease of heart or aorta.

Hypertension alone or when associated with some other condition produces increase in the size of the shadow of the width of the arch in 60 per cent to 65 per cent of the cases. When both hypertension and arteriosclerosis are present, the figure mounts to 79 per cent, being exceeded only by luetic aortitis.

CONCLUSIONS

The formula of Hodges and Eyster is the most efficient standard in predicting the transverse diameter of the normal heart.

A heart whose transverse diameter exceeds the predicted diameter by more than 1.0 cm. should be considered enlarged.

In subjects under sixty years of age there is an average width of the aortic arch in accordance with age and sex. This measurement increases with age and is larger in the male than in the female of the same age.

When the average width for the age and sex is exceeded by more than 0.5 cm., the chances are 87 per cent in favor of a pathological cause for the increase in the measurement.

NOTE.—All measurements in this study were obtained by orthodiagraphy with the subject erect.

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A CASE OF TETRALOGY OF FALLOT: CLINICOPATHOLOGICAL OBSERVATIONS; QUANTITATIVE STUDIES OF CIRCULATION RATE AND THE RIGHT-TO-LEFT SHUNT*

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INTRODUCTION

THERE are a number of types of congenital heart disease which cause marked cyanosis; of the cases which live to the age of puberty or early adult life, the so-called tetralogy of Fallot is the most common. This consists of pulmonary stenosis, defect of the interventricular septum, right ventricular hypertrophy and "rechtslage" of the aorta. Our knowledge of the clinical course and pathological anatomy of this lesion-complex has been built up from the analysis of cases that have accumulated in the literature. Further intelligence of this condition must also depend largely upon this method; for, though the tetralogy of Fallot is one of the more common forms of congenital heart lesions, it occurs relatively rarely in the experience of any one individual.

The progress in the study of the physiology of circulation in man that has been made within recent years now makes it possible to analyze the pathological physiology of the circulation in these cases. Such analyses are of considerable significance, both academically and practically. The abnormal conditions present in the tetralogy of Fallot could hardly be reproduced experimentally in animals, and they offer excellent opportunities for studying the adaptation of the body to high grades of oxygen unsaturation. From the practical, clinical point of view, facts about the pathological physiology of these cases may become of value in prognosis. It therefore seems logical to insist that every case of this sort, as of other types of congenital heart disease, should be intensively studied and fully reported, in order to make the case available for the investigator who might undertake to assemble and correlate the accumulated knowledge.

The case which is the subject of this report is that of a young man who died at the age of twenty-three years. He first came to the Montreal General Hospital in November, 1919, at the age of seventeen years, and was subsequently observed in the out-patient department and in the wards of the hospital until the time of his death. The progress of his condition was carefully observed clinically; and during the second and third of his four

*From the Medical Service of Professor C. P. Howard and the Cardiac Clinic, Montreal General Hospital. At the request of Professor Howard and with the kind permission of other members of the staff, who recorded their observations and studies in this case, and of Dr. Maude E. Abbott, who performed the autopsy, the author has collected and correlated all the available data.

periods of stay in the hospital, physiological studies of his circulation were made by Dr. I. M. Rabinovitch.

I. M., male aged seventeen years, born in Russia of Jewish parents; migrated to Canada at the age of five years; came to the hospital's out-patient department and was admitted to the medical service of Dr. H. A. Lathur on November 18, 1919. He complained chiefly of dyspnea on exertion and dull pain in both axillae. He had been born a blue baby and remained blue, but his physical stature developed normally. He had had dyspnea on exertion ever since childhood. He could never play actively with other children. He received private tuition from the age of seven years and began to attend school at the age of twelve, but made very slow progress in his studies: he could not learn to read or write. At school he was allowed to walk to and from classrooms and to perform other necessary physical exertion at his own slow pace. Of late he had been getting weaker generally and more dyspneic: he had also begun to experience a constant dull ache in each axilla and had developed a cough which was usually unproductive but sometimes brought up whitish, and occasionally blood-stained sputum. On November 14, 1919, he had to stop going to school because of these symptoms.

Neither he nor the members of his family recall his having suffered from any infections or other disease. His mother is alive and well; his father has emphysema; five sisters died, one of peritonitis, the other four of unknown causes.

Physical Examination.—The patient presented the picture of a markedly cyanotic youth; he had a large nose, thick nostrils and lips, large hands with large clubbed fingers, large feet with markedly clubbed toes. His poor personal hygiene and general behavior suggested that he was a mental deficient. Breathing was somewhat labored, but there was no evidence of orthopnea. Conjunctival vessels were dilated and prominent. The teeth were carious and there was much pyorrhea. The palate was highly arched. The throat was injected; the tonsils were not diseased. Some fine crepitations were heard in each axilla; examination of the lungs was otherwise negative.

Heart.—Maximal apex impulse felt in fifth left interspace 10 cm. from the mid-sternal line; at the base a pronounced systolic thrill was felt with maximum intensity in second left interspace near the sternum. Relative cardiac dullness extended 6 cm. to right and 10 cm. to left of midsternal line in fifth space; there was no increase in supra-cardiac dullness. Heart sounds were heard with fair intensity at the apex: a rough systolic murmur was traced from the apex to the second left interspace where it was loudest; it was harsh and masked the first sound. This murmur was heard over the entire front of the chest and also over the back: it was not heard over the carotid arteries. The second sound was loud over the aortic area and faint over the pulmonary area. Cardiac rhythm was normal. Systolic blood pressure 152, diastolic 100 mm. Hg. The liver edge was not felt, but liver dullness extended to 4 cm. below the right costal margin in the mammary line. There was no ascites. Moderate-sized lymph glands were felt in the cervical, axillary and inguinal regions. There was slight edema of the lower extremities. Cranial nerve reflexes were normal. There was sustained ankle and rectus clonus. The ocular fundi showed dilated full veins; no pulsation of these was seen.

Blood Examination.—November 18, 1919. Red cell count 7,350,000; white cell count 14,000; hemoglobin, 104 per cent. Differential count: polymorphonuclears 81 per cent, lymphocytes 18 per cent, eosinophiles 0.3 per cent.

X-ray pictures of hands showed increase in soft tissues around terminal phalanges, but no bony changes.

Electrocardiogram: Sinus arrhythmia, rate 75, marked right axis deviation.

Urine: Frequent examinations showed constant presence of albumin varying in amount from a slight trace to a strongly positive evidence.

November 21. At midnight patient had a convulsion; complained of severe headache before and after the convulsion.

November 22. Severe headache continued: 200 c.c. blood drawn from median basilic vein gave him some relief. There was incontinence of urine and feces, apparently due to mental deficiency. Blood pressure 152 systolic, 100 diastolic. (Foul odor to breath.)

November 23. Severe headache continued; patient very restless; occasional vomiting; incontinence of urine and feces; had a convulsion at 5:30 P.M. Lumbar puncture: clear fluid drained under great pressure caused no relief of headache. Examination of spinal fluid: Noguchi, Nonne and Pandy tests all positive.

November 24. As on previous day. Twitching of eyes and face noted. Systolic blood pressure 148.

November 25. Very noisy; attempted to get out of bed; headache seemed less severe.

November 28. He was quiet; headache was milder; red cell count 6,680,000; white cell count 10,000; hemoglobin 106 per cent. Blood pressure 136 systolic, and 106 diastolic.

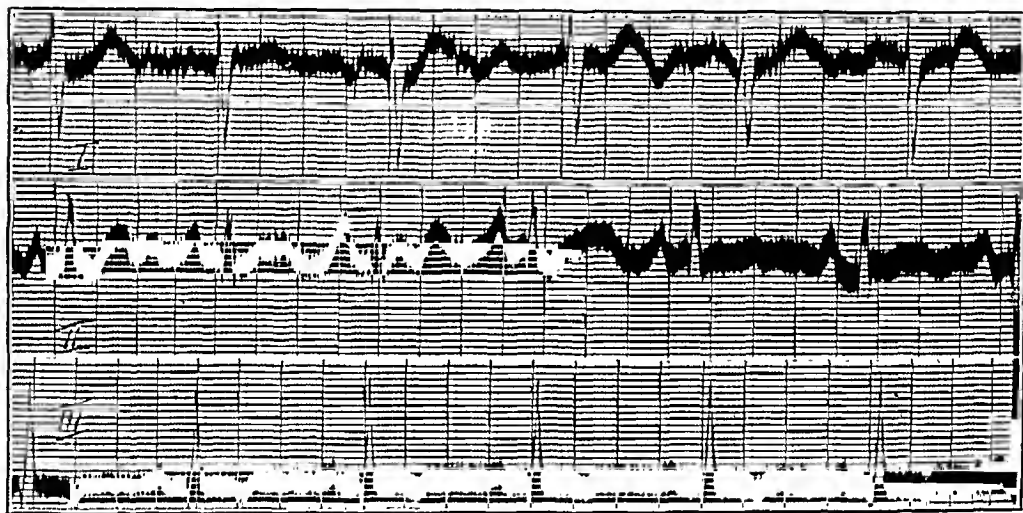


Fig. 1.—Electrocardiogram taken March 7, 1923. Normal rhythm; rate 75; P-R interval 0.21 sec.; P₂ equals 0.5 millivolt and 0.12 second; marked right axis deviation; respiratory variations in height of P-wave.

November 30. No headache; urine incontinence only once; systolic blood pressure 120.

December 7. Headache and vomiting had ceased; felt well; discharged from hospital.

Diagnosis.—Congenital malformation of the heart.

He visited the outpatient department several times in the next three years, and on March 17, 1923, he was readmitted to the hospital under the care of Dr. F. G. Finley. His main complaint was that of diffuse abdominal pain about which no satisfactory history could be elicited. Physical examination revealed some enlargement of liver and spleen; the physical signs of the cardiovascular system were similar to those of 1919; extrasystoles were observed; the blood pressure was 104 systolic and 74 diastolic; there was no edema of extremities. The red cell count was 7,400,000 and the white count 6,500. He remained in the hospital for three weeks during which the abdominal symptoms disappeared.

On November 26, 1924, he entered the hospital under the care of Dr. C. P. Howard. A new symptom was the occurrence of spells of dizziness without loss of consciousness, and no signs suggestive of epilepsy: each attack lasted five or ten minutes, and the

attacks occurred almost daily. These symptoms first appeared in June, 1923. In October of that year he had a bad cold for three weeks during which he coughed up blood-stained sputum.

On November 29, Dr. Howard made the following notes: "The patient presents a most marked grade of cyanosis; it is generalized but, of course, chiefly in the ears, lips, nose, fingers and toes. There is also injection of the conjunctival vessels. The drumstick (clubbed) fingers and toes are very pronounced, the enlargement being largely venous. The nail beds are of a sky blue shade and more intensely blue than the skin of the fingers; the nails are curved and show atrophic changes with dark pigmented areas near the free margins. There is some enlargement of tibiae and fibulae and also to a lesser degree of the radii and ulnae. The bases of the lungs seem quite clear on percussion and auscultation. The thorax shows no precordial bulging;

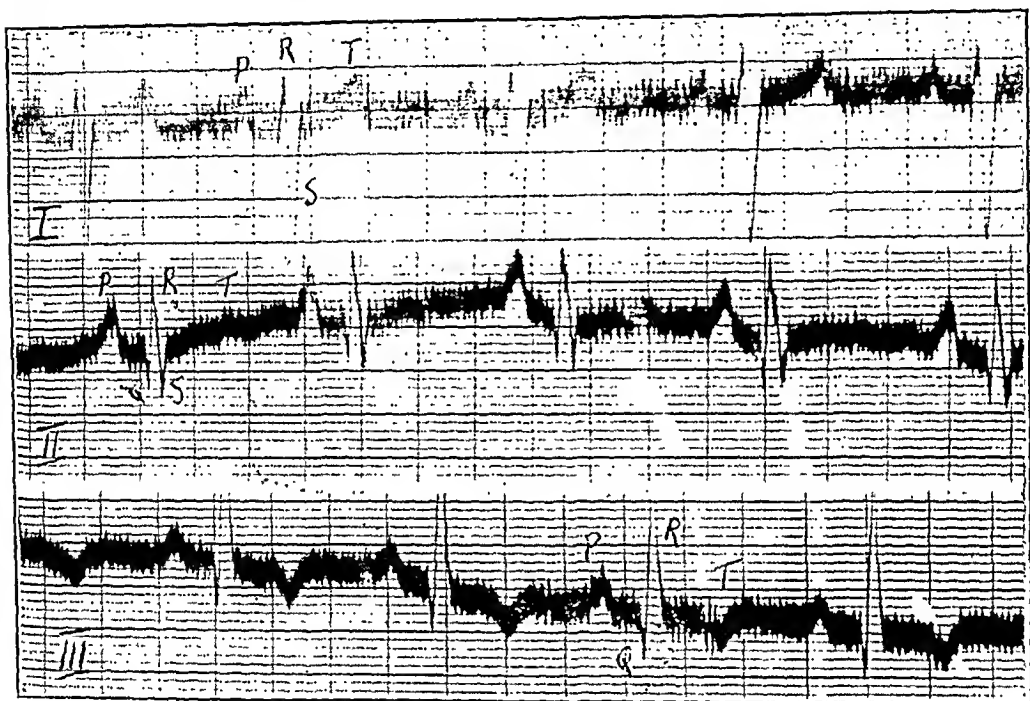


Fig. 2.—Electrocardiogram recorded December 1, 1924; normal rhythm; rate 75; P-R interval 0.2 second; P_r 0.4 millivolt and 0.10 second in duration; marked right axis deviation; premature beats observed but not recorded.

if any asymmetry exists it is due to preeordial retraction: the sternum and costal cartilages project prominently. There is no special pulsation visible at apex or base. The maximal apex impulse is palpable in the fourth left intercostal space 8.5 cm. from the midsternum. At the mitral area the systolic shock is felt but there is no thrill. There is a suspicion of a thrill in the second and third left interspaces near the sternum. Over the great vessels there is a well felt diastolic shock. Relative cardiac dullness: upper border over second left interspace; 5.3 cm. to the right and 10.5 cm. to the left of the midsternal line in the fifth interspace. X-ray plate shows enlargement of heart shadow to the right. Heart action is regular and slow. At apex a faint systolic murmur and a very faint diastolic murmur are heard; over the tricuspid area both these murmurs are louder; they are, however, best heard in the second and third left intercostal spaces near the sternum. The second sound is loud and of equal intensity over the pulmonic and aortic areas. The radial pulses are synchronous and equal. The liver just reaches the right subcostal margin; it is not enlarged and not tender. The spleen is moderately enlarged, firm, but not tender."

On December 11 he had an attack of loss of consciousness which was described as follows by Dr. E. S. Mills: "After supper, while the patient was sitting in a chair, he suddenly felt dizzy, then fell to the floor with convulsive movements of the arms and legs, frothing at the mouth, coughing and expectorating small quantities of bright red blood. He was put to bed by attendants. When seen, about a minute after the onset, he was found lying in bed, unconscious; respirations were deep and rapid, blood-tinged froth oozed from the mouth. The pupils were dilated and fixed. The knee jerks were absent and the arms and legs in a state of flaccid paralysis. In about five or six minutes he began to make efforts to get out of bed, and resisted as the blood pressure was being taken. This was found to be 148 systolic and 110 diastolic. Consciousness slowly returned, the knee jerks became active, and the pupils assumed their natural size. During this attack the cyanosis was most intense. He had never had such an attack before."

During this period of stay in the hospital a number of laboratory procedures done on previous occasions were repeated.

The electrocardiogram (Fig. 2) showed normal rhythm, rate 75, marked right axis deviation; high P-wave in Lead II, and slurring and notching of the R-wave in Lead II. Some extrasystoles, most probably auricular, were observed but not recorded.

X-ray examination of the heart (November 28, 1924) revealed an increase in the transverse diameter of the heart, especially to the right, and the left auricle also appeared enlarged. X-ray examination of the hands showed, as before, fullness of the soft tissues overlying the distal phalanges. There were no bone changes and the knees were perfectly normal.

Wassermann reaction of the blood was negative. November 29, 1924: Red blood cells 9,200,000; white blood cells 8,600; hemoglobin 146 per cent (calculated from oxygen capacity). December 2, 1924: Red blood cells 10,280,000; hemoglobin 205.5 per cent (calculated from oxygen capacity determined by Dr. Mills). Hematocrit 0.775. January 7, 1925: Red blood cells 9,090,000; hemoglobin 187.2 per cent (calculated from oxygen capacity of the blood determined by Dr. Mills on the basis 18.5 c.c. O_2 = 14 gm. Hb.).

November 28, 1924: Blood urea nitrogen 17.0 mg.; and sugar 0.125 mg. per 100 c.c. blood. Frequent examinations of urine showed the specific gravity to vary between 1.018 and 1.021, few pus cells and phosphates in the sediment, but no albumin, sugar or casts.

December 1, 1924: Dr. I. M. Rabinowitch made observations required for calculating the circulation rate; these are described below.

January 27, 1925: Dr. E. S. Mills made the following notes: "The patient has been up and about in the ward for the past three weeks. He has suffered from frontal headaches from time to time, but on the whole has enjoyed fairly good comfort. His appetite is good, bowels are regular. He now has no dyspnea at rest. There has been no apparent change in the degree of cyanosis. Physical examination: lungs clear; heart—apex impulse in fifth left intercostal space 8 cm. to left of midsternal line. Relative cardiac dullness begins at third left rib, and in fifth space extends 9 cm. to the left and 5.5 cm. to the right of the midsternal line; there is a faint thrill in the second and third left intercostal spaces; the heart sounds are as on admission. There is no edema of the extremities. The patient is discharged from the hospital to go to his home."

November 25, 1925: The patient was readmitted to Dr. Howard's service. He complained of marked dyspnea on exertion; he could not walk one hundred yards without having to "stop for breath" and he has been using three pillows to sleep on, to avoid the dyspnea he has on lying flat. The seizures of dizziness and unconsciousness have increased very much in frequency; he was free from them for the first four months after leaving the hospital in January, 1925, they then began to come on again and

finally occurred once or twice daily. They occur only during the daytime, usually when he is standing; he has never had one at night while lying in bed. The occurrence of a seizure bears no definite relation to any of his habits or activities. He has lately suffered severely from supraorbital headaches; there has been some conghing, but without expectoration. His hands and feet are always cold, but he has not experienced any numbness. For many months he has not stirred out of the house for fear of having a fit while on the street. Physical examination revealed signs similar to those of November, 1924.

November 30, 1925: While in bathroom he vomited and felt faint; he was found unconscious, very deeply cyanosed and breathing stertorously; pupils at first were dilated, did not react to light. The abdominal reflexes could not be elicited but the tendon reflexes were all present; there was no spasticity nor any undue degree of flaccidity. There was no biting of the tongue and no frothing at the mouth. Blood pressure 110 systolic and 60 diastolic; pulse 72 per minute and irregular. The attack lasted ten

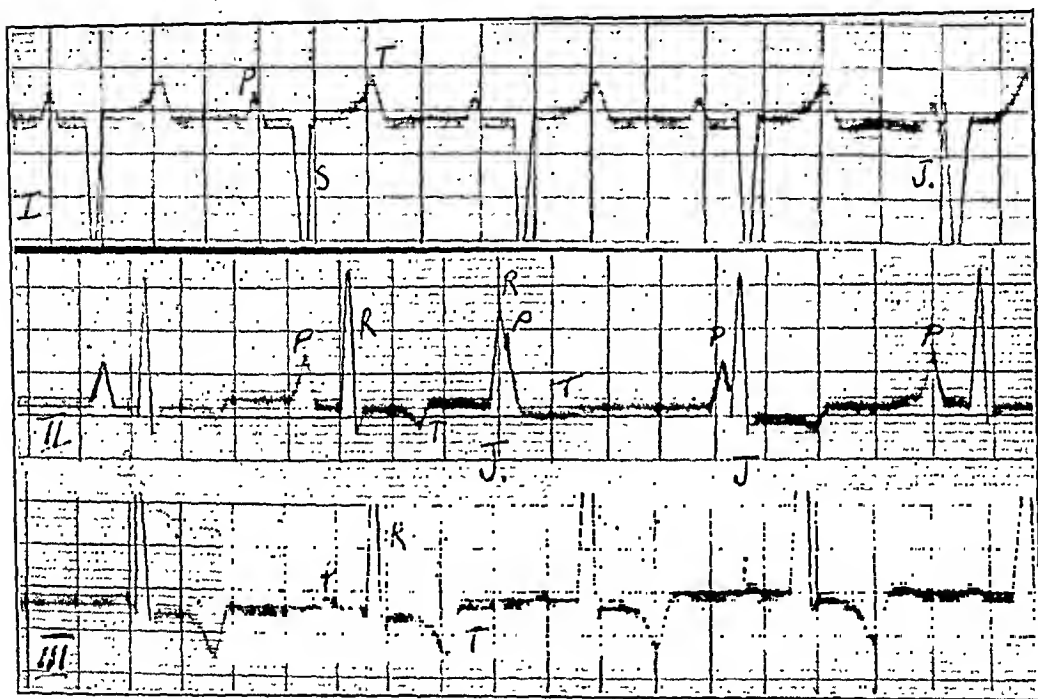


Fig. 3.—Electrocardiogram taken December 1, 1925. Normal rhythm interrupted by premature beats originating at different points in junctional tissue marked "J," in Leads I and II; rate 75. The P-R interval 0.2 second; the P-wave in Lead II is 0.5 millivolts and 0.1 second; marked right axis deviation.

minutes, the patient after regaining consciousness was apparently very much weakened for he soon fell asleep. Otological examination on this day revealed bilateral otitis media.

December 4, 1925: The patient seemed more comfortable in the past four days. Occasional extrasystoles were detected. Oxygen administered by funnel method for fifteen minutes did not lessen cyanosis to any appreciable degree.

December 5, 1925: Inhalation of oxygen under pressure for thirty minutes caused no change in cyanotic color.

Blood examination November 25, 1925: Red blood cells 8,100,000; white blood cells 9,300; hemoglobin 120 per cent (Dare).

December 4, 1925: Red blood cells 8,630; white blood cells 6,850. Differential count: polymorphonuclears 76 per cent, large lymphocytes 4 per cent, small lymphocytes 17 per cent, eosinophiles 3 per cent. No abnormalities in shape of red cells.

Hemoglobin 194.7 per cent (van Slyke). Urea concentration factor (Rabinowitch) equals 41. Urea nitrogen 20. Creatinin 1.76. Oxygen capacity of blood 36.02 vols. per cent.

December 8, 1925: The following note was made by the house officer, Dr. Webster: "At 8 P.M. patient was sitting up in bed, apparently feeling better than during the



Fig. 4.—A, superior vena cava; B, inferior vena cava; C, patent foramen ovale; D, sinus coronaris (anomalous tendinae replacing thebesian valve); E, right ventricle seen through defect; F, conus arteriosus.



Fig. 5.



Fig. 6.

Fig. 5.—The conus arteriosus (showing fused semilunar valves, the raphes at A, B, and C).

Fig. 6.—The left ventricle, showing partial fusion and ulceration of the semilunar valves of the aorta, which roof the defect in the interventricular septum.

past few days. Suddenly the nurse noticed blood coming from his mouth. The patient called to her and shortly afterward lapsed into one of his typical fits of unconsciousness. He had incontinence of urine and feces, his teeth were clenched and the pupils dilated. The first hemorrhage consisted of about 8 ounces of frothy red blood. At about 8:15 P.M., while still unconscious, he had a second hemorrhage. About four ounces of frothy (pulmonary) blood issued from the nose because of the clenched teeth firmly closing his mouth. The patient did not regain consciousness, the jaws remained rigid." Thus the patient died.

SUMMARY OF POST-MORTEM REPORT

Autopsy was performed and findings were described in full detail by Dr. Maude E. Abbott.

Summary:

1. General congestion and cyanosis of all tissues.
2. Marked clubbing of all fingers and toes with incurving nails.
3. Foramen of Winslow obliterated.
4. Lesser peritoneal cavity closed by adhesions.
5. Enlarged liver, congested and firm.
6. Hypertrophied kidneys, with cortex-medulla ratio increased.
7. Markedly hypertrophied and congested spleen.
8. Great distention of stomach with black tarry material.
9. Marked hypostatic congestion.
10. Evidence of pulmonary hemorrhage in both lungs, with blood-filled bronchi.
11. Heart: This case presents a classic example of the so-called tetralogy of Fallot, in which a pulmonary stenosis and hypoplasia of the developmental type is associated with a defect of the interventricular septum just anterior to the undefended space, and with dextra-position of the aorta which rides above the defect, receiving the blood from both ventricles; and this combination is the commonest condition in cases of congenital cyanosis with clubbing reaching adult life. The chief points of additional interest are, the compensatory changes in the infundibular cusps of the tricuspid valve, the sclerosing process on the conus wall and pulmonary and tricuspid valves, and the inflammatory fusion of aortic cusps with recent endocarditis; also the dilatation of the ascending aorta with hypoplasia of the trunk below in the absence of coarctation.

DETERMINATION OF THE VENOUS ARTERIAL SHUNT

The observations presented in Table I and the calculations described in Table II were made by Dr. I. M. Rabinowitch.

Calculation of the Venous Arterial Shunt

Let X = shunt, expressed in per cent of total cardiac output.

a = reduced hemoglobin content of arterial blood.

V = reduced hemoglobin content of venous blood.

T = total hemoglobin (100 per cent).

p = reduced hemoglobin in pulmonary vein blood.

Then

$$a = (1 - X) p T + X V.$$

For the value of V either v_1 , the reduced hemoglobin content of arm vein blood, or v_2 , that estimated for mixed venous blood, may be used.

DISCUSSION

The Venous Arterial Shunt.—The clinical and anatomical features of the tetralogy of Fallot obviously indicate that during life the arterial

TABLE I

		MAR. 16, 1923		DEC. 1, 1924
		BASAL	AFTER EXERCISE	BASAL
A	Oxygen content of arterial blood	7.32 vols. %	5.16 vols. %	16.9 vols. %
A ₁	Oxygen capacity of arterial blood	21.96 vols. %	21.96 vols. %	26.3 vols. %
a	Reduced hemoglobin in arterial blood	66 %	76.5 %	35.8 %
V ₁	Oxygen content of arm vein blood	3.82 vols. %	0.66 vols. %	9.8 vols. %
v ₁	Reduced hemoglobin in arm vein blood	83 %	97 %	62.8 %
V ₂	Oxygen content of mixed venous blood (A-5) *	2.32 vols. %	0.16 vols. %	11.9 vols. %
v ₂	Reduced hemoglobin of mixed venous blood	89.95 %	99.27 %	55 %
P	Oxygen content in pulmonary vein blood (.955A ₁) †	20.97 vols. %	20.97 vols. %	25.1 vols. %
p	Reduced hemoglobin in pulmonary vein blood	0.045 %	0.045 %	0.045 %
	Oxygen consumption per minute	241.0 c.c.	328.0 c.c.	281.0 c.c.
	Metabolic rate	+7 %		+22 %

*5 vols. % is assumed to be the amount of oxygen utilization in the tissues according to Lundsgaard.

†It is assumed that the process of oxygenation in the lungs is normal.

TABLE II
EQUATION OF VENOUS ARTERIAL SHUNT

	MAR. 16, 1923		DEC. 1, 1924
	BASAL	AFTER EXERCISE	BASAL
$a = (1 - X) p T + X v_1$	78.3%	77.85%	53.7%
$a = (1 - X) p T + X v_2$	72%	75.8%	62.0%

stream consists of a mixture rich in reduced hemoglobin. The exact proportions of reduced and oxygenated hemoglobin in this mixture must vary in different individuals under similar conditions of body activity, depend-

ing upon the relative size of the pulmonary and aortic orifices, the size of the septal defect and the position of the aortic orifice in relation to its communications with the right and left ventricular cavities. Other factors, such as the efficiency of ventricular musculature, the influence of associated anomalies, as, for example, collateral pulmonary circulation through bronchial arteries, patent ductus arteriosus, patent foramen ovale, hypoplasia of the aorta, etc., must also play important rôles in determining the nature of the mixed blood in the arterial stream. One may therefore expect to find differences in the estimates of the arteriovenous shunt made in different cases. We have been able to discover reports of such studies in but six cases.

The first report of circulation rate studies and estimation of the venous arterial shunt in a case of tetralogy of Fallot is that of Weiss and Löwbeer² (1924). Abbott³ quotes a case investigated at the Massachusetts General Hospital by Bock, Field and Stoddard in 1924. The observations in our case were made by Dr. I. M. Rabinowitch in 1923 and 1924; our case is the only one in which an attempt was made to observe the effects of exercise on the circulation rate and on the shunt. Dautrebande, Marshall and Meakins¹ (1929) report studies on three cases in one of which observations were made in 1922. Richards, Riley and Hiseock,⁴ in the most recent report, include studies of the effect of keeping the patient in an oxygen chamber, but do not calculate the shunt. Abbott quotes the data and methods of calculation described by Weiss and Löwbeer and by Bock and his associates. Dautrebande, Marshall and Meakins calculated the venous shunt by the two methods of Bock and his associates in two of their cases and by all three methods in the third case; the results varied so widely that they concluded "it was found impossible to obtain reliable determinations of the venous, or right to left, shunt." We have applied additional methods of calculating the shunt to the data of Weiss and Löwbeer's case and of our case and have tabulated the results obtained by various methods in the six cases (Table IV). In only one of the cases in the series of Dautrebande, Marshall and Meakins were data available for the application of the Weiss and Löwbeer method. In all cases the data permit calculation of the shunt by the following equation.

$$A = \frac{V}{100} + \frac{P(100 - X)}{100}$$

in which $A = O_2$ content of arterial blood
 $V = O_2$ content of venous blood
 $P = O_2$ content of pulmonary vein blood.

In each case (A) the O_2 content of radial artery blood was determined directly. For the O_2 content of venous blood either of two values is available, namely, (V_1) the oxygen content of arm vein blood determined by experiment, or (V_2) the assumed mixed venous blood value calculated by

subtracting 5 vols. per cent from the arterial O_2 content (Lundsgaard and van Slyke,⁵ average oxygen utilization by the tissues is 5 per cent). For estimating the O_2 content of pulmonary vein blood it is also possible to choose between two values; it may be assumed that oxygenation proceeds normally so that the blood entering the pulmonary veins is 95.5 per cent saturated (P_1) or the observations of Campbell, Hunt and Poulton⁶ may be taken into consideration and the blood may be assumed to be 85 per cent saturated (P_2). Thus, using the above formula, four different calculations of the shunt may be made in each case, thus—

1. $A = 0.01 (V_1)X + (100-X) (0.01)P_1$
2. $A = 0.01 (V_2)X + (100-X) (0.01)P_1$
3. $A = 0.01 (V_1)X + (100-X) (0.01)P_2$
4. $A = 0.01 (V_2)X + (100-X) (0.01)P_2$

TABLE III

VENOUS ARTERIAL SHUNT CALCULATED BY FOUR DIFFERENT EQUATIONS

EQUATION	MARCH 16, 1923		DEC. 1, 1924
	BASAL	AFTER EXERCISE	BASAL
1	79.5%	77.8%	53.4%
2	73.0%	76.0%	62.0%
3	76.4%	75.0%	43.4%
4	69.3%	73.0%	52.2%
Maximum % variation	14.5%	8%	42.8%
Minimum % variation	2%	1.3%	2.2%

The differences in the estimated shunt depending upon the nature of the assumptions made in the calculation, the four equations were applied to the data of our case (Table III). Equations 1 and 2 are those used by Boek, Field and Stoddard³ in two separate experiments. In all of the cases the data allowed calculation of the shunt by equation 2 (Table IV), with the exception of the Weiss and Löwbeer² case and one of the two experiments in the case of Boek and his associates equation 1 could also be applied.

The equation used by Rabinowitch for the calculation of the shunt in our case is the same as that of Boek, Field and Stoddard, only Rabinowitch applies the values for reduced hemoglobin instead of those for oxygenated hemoglobin. Hence calculations by the method of Rabinowitch lead to results essentially the same as those of equations 1 and 2.

A comparison of the results obtained in each case by different methods of calculation (Table IV) reveals variations that range between 2 and 215 per cent. If the results are viewed in the light of these two extremes, Dautrebande, Marshall and Meakins may be considered as justified in concluding that no reliable calculation of the shunt could be made. The

instance of 215 per cent variation occurs in one of their cases. All the other cases also show such wide variations that one must question whether these estimates of the shunt have any significant value. On the other hand, the estimates made with equation 2* present figures which seem to represent the magnitude of the venous arterial shunt quite reasonably when due allowance is made for anatomical differences in the different cases. Furthermore, at present, equation 2 seems to offer the most reliable formula for calculating the shunt, since the possible errors in the data required are smaller than in either of the other two formulae. Thus in equation 1, the oxygen content of arm vein blood is used to represent that of mixed venous blood in the right auricle. Now it has been shown by a number of observers that the oxygen content of arm vein blood is likely to vary widely and that it is not truly representative of mixed venous blood. A crucial factor of the Weiss and Löwbeer² method is the estimation of the pulmonary blood flow by the nitrous oxide method; the experimental error of this procedure is so great as to make it unsuitable for the quantitative estimation of total circulation and of the shunt in a given case, although it may be of value for studies of a comparative nature. The sources of error for all methods seem to be in the limitations of the technic of measuring cardiac output in man rather than in the validity of the equations. Table III illustrates the wide variations in the figures of the estimated shunt when different assumptions are made as regards oxygen content of mixed venous blood and of pulmonary vein blood. The greater uniformity of the figures obtained with equation 2 is due to the fact that the two most important factors in the data required were obtained by a technic that may be said to have a low experimental error even when used by different individuals; the quantitative estimation of the oxygen content of the mixed venous blood is obtained by assuming the oxygen utilization to be 5 vols. per cent.

The clinical and pathological features of the tetralogy of Fallot offer evidence from which one may deduce an approximate estimate of the proportions of "venous" and "arterial" blood which make up the mixture that enters the aorta from the heart. The large right chambers and the relatively small left chambers of the heart indicate that the output of the right heart is much greater than that of the left. Second, the position of the aortic orifice and its patent communication with the right ventricle, and on the other hand, the smallness of the pulmonary orifice and the high resistance at this aperture, point to a generous flow of "venous" blood into the aorta. Basing an estimate of the amount of venous blood that enters the aorta on these considerations it may be judged to be 50 per cent or more of the total cardiac output. It, therefore, seems to be a significant fact that the values obtained by the application of equation 2 to the data in

*Dr. Maude E. Abbott has drawn my attention to the fact that in 1924 Dawson¹² suggested the method of calculation represented by this equation on purely theoretical grounds.

the different cases range between 45.4 per cent and 76 per cent. It now appears reasonable to consider the magnitude of the venous arterial shunt, under basal conditions, to be at least 40 per cent of the total cardiac output into the aorta.

Clinical observers have invariably described an increase in cyanosis on exertion in cases of tetralogy of Fallot. With increase in cardiac output per minute during exercise it is most likely that the free communication between the right ventricle and the aorta and the very restricted communications with the pulmonary circulation make for an increase in the proportion of venous blood in the arterial stream. Another likely factor in the production of this increase in cyanosis is the acceleration of oxygen utilization in the tissues as a compensatory mechanism. Thus the proportion of reduced hemoglobin in capillary blood must become considerably increased. The single determination of the effect of exercise in our case reveals a relatively small increase in the shunt by equation 2, and a very small diminution by equation 1; the former figure seems to be the closer approach to the truth, although the increase is smaller than one might expect to find.

During the last six months of the life of our patient there was striking progressive increase in cardiac failure: orthopnea appeared, he suffered from attacks of pulmonary congestion similar to those met with in cases of mitral stenosis, and he died in the course of one of these attacks. The last experiment for the estimation of circulation rate and venous arterial shunt was performed about a year before his death; therefore in comparing the results of this experiment with those of the first data obtained twenty months previously, it becomes necessary to consider the factor of diminished myocardial strength, especially of the right ventricle. The venous arterial shunt estimated in December, 1924, is at least 15 per cent smaller than that determined in March, 1923. This diminution may be attributed to a disproportion in the myocardial failure of the two ventricles. As the right ventricle loses strength in greater degree than the left, the venous arterial shunt also diminishes. However, the total cardiac output also becomes decreased and pulmonary circulation becomes less efficient so that in spite of the relatively smaller shunt the circulatory mechanism is weakened.

Circulation Rate.—The amount of blood put out by the heart into the aorta per minute may be estimated by applying the following equation:

$$C = \frac{M}{U} \times 100$$

wherein C = circulation rate, M = oxygen consumption per minute expressed in cubic centimeters, and U = the oxygen utilized by the tissues expressed in volumes per cent. The value for U may be taken as 5 (U₂) according to Lundsgaard and van Slyke⁵ or it may be calculated as the dif-

ference (U_1) in oxygen content between the arterial and arm vein bloods determined by experiment. Using U_2 , the circulation rates in cubic centimeters per minute, determined in our case are 4,820 at rest, 6,560 after exercise in March, 1923, and 5,620 at rest in December, 1924. Using U_1 , the corresponding rates are 6,887, 7,288 and 4,014 respectively. The increase following exercise is within expected limits. The rates for basal conditions estimated from the experiments in 1923 and 1924 are so discordant that they cannot be compared logically. It is more likely that as the result of right ventricular myocardial failure, evidenced by the clinical observations and by the diminution in the venous arterial shunt, the total circulation rate was smaller in December, 1924, than twenty months previously when cardiac function was more efficient. Weiss and Löwbeer² estimated the circulation rate as 7,080 c.c. per minute in their case, under basal conditions; this is a somewhat higher figure than any of ours.

TABLE IV

VENOUS ARTERIAL SHUNT CALCULATED BY DIFFERENT METHODS, EXPRESSED IN PER CENT OF TOTAL CARDIAC OUTPUT

CASE	EQUATION NO. 1	EQUATION NO. 2	WEISS AND LÖWBEER	VARIATION	
				MAXIMUM	MINIMUM
Dautrebande et al. ¹	40.5	68.8		70	41.0
Dautrebande et al. ¹	34.0	58.0		70	41.0
Dautrebande et al. ¹	19.8	45.4	62.4	215	27.2
Weiss and Löwbeer ²		56.2	69.0	23	10.8
Bock et al. ⁴ Jan. 15, 1924		70.7			
Bock et al. ⁴ Jan. 21, 1924	69.2	48.83		41.7	29.0
Our case Mar. 1923, Basal	79.5	73.0		8.8	8.3
Our case Mar. 1923, Post exercise	77.8	76		2.37	2.31
Our case Dec. 1924	53	62		17.0	14.5

Growth and Development.—The mother of our patient has told us that he was blue from birth onwards, but that he grew in stature quite normally and, moreover, that he was physically strong. Mentally, however, he was very different from the other children in the family. He was given private tuition at home and also attended school, but was unable to learn the most elementary things and grew up illiterate, although he was intelligent enough to understand and carry out simple commands as well as to attend to his personal needs. He made himself useful in helping his father attend to the chores of a small grocery shop, but was unable to assist in waiting upon customers. The question as to whether the mental deficiency might be attributed to the cause of the marked cyanosis is suggested by the fact that Haldane⁷ describes psychic effects including mental dullness during relatively high grades of anoxemia. The adaptation of the tissues to low

oxygen saturation of the blood in our case will be discussed below; it will then become apparent that the degree of cyanosis is not a true measure of anoxemia and that the tissues were provided with sufficient oxygen to maintain normal body metabolism within certain limits of activity. Dr. Maude E. Abbott, from her intimate knowledge of the literature, as well as from personal experience of similar cases, has gained the impression that patients with congenital cyanosis are usually of normal and, not infrequently, of supernormal intelligence. The subject of Bock, Field and Stoddard's observations, whom one of us (H. N. S.) observed during life, was a man of thirty-two years, with cyanosis and heart similar to that of our case; he was unusually bright as a business man and very witty. There seems to be no direct relationship between the cyanosis and mental deficiency in our case.

Adaptation of the Body to the Cardiac Anomaly.—The intense grade of cyanosis from birth suggests a very grave degree of oxygen want, so that one would expect stunted growth in body and mind in these cases. The fact that they are usually normal in this respect indicates the high degree of adaptation to the pathological condition that causes the cyanosis. Another remarkable feature of these cases is that many survive to the age of puberty and not a few go beyond the second and third decades. An analysis of all the factors concerned in the adaptation of the functions of the body to abnormal conditions of circulation must necessarily be limited at the present time for want of knowledge.

In the heart itself, the congenital pulmonie stenosis is accompanied by a compensatory hypertrophy of the right ventricle. In our case, this was diagnosed clinically on ample grounds, namely, enlargement of the heart to the right as determined by percussion and x-ray examination, and in addition, marked right axis deviation shown in the electrocardiogram. The post-mortem examination showed a very thickened and enlarged right ventricle, and a less thick and smaller left ventricle. This cardiac hypertrophy, particularly of the right ventricle, is the chief mechanical factor of adaptation; in virtue of it the lungs received relatively sufficient blood in spite of the small pulmonary valve orifice. A conservative estimate of the circulation rate, under basal conditions, was determined as 4820 c.c. per minute on one occasion, and 5620 c.c. on another, whereas after exercise it was found to be 6560 c.c. per minute. These figures closely resemble those obtained in the normal and thus indicate that the cardiac hypertrophy was quite effective in compensating for the mechanical disabilities.

The next obvious factor of adaptation is the marked degree of erythrocytosis; in our case there was an increase of 50 to 100 per cent in red cells without a corresponding increase in white cells, and a hemoglobin content always more than 100 per cent. On one occasion the hemoglobin content was calculated from the oxygen capacity of the blood and found to be 194.7 per cent, with a red cell count of 8,630,000; and on another occasion

205.5 per cent, with a red cell count of 10,280,000. From studies of the adaptation of normal individuals to living in high altitudes, it has long been known that an increase in red cells and hemoglobin takes place in order to compensate for the lower partial pressure of oxygen in the atmosphere. An individual who is not adapted to high altitudes presents symptoms of anoxemia when exposed to a lowered partial pressure of oxygen, that is to say, symptoms of want of oxygen in the body tissues. In a case of tetralogy of Fallot, the right-to-left shunt results in an admixture of "venous" and "arterial" blood which reduces the oxygen content of the mixed blood considerably below that of "arterial." Thus the blood of the systemic arterial stream is characterized by a sufficiently low oxygen content to cause marked cyanosis. But the basal metabolic rate measured on two occasions in our case was +7 and +22 per cent; in other words, the body tissues were being supplied with ample oxygen and were not suffering from anoxemia. It appears, therefore, that the degree of cyanosis is no index to the degree of anoxemia in a case such as ours. The increase in the number of red cells and the amount of hemoglobin raises the oxygen capacity of the blood so that it becomes possible to maintain an oxygen tension in the capillaries sufficiently high to provide the tissues with their normal oxygen requirement within certain limits of body activity.

The duration of life in 73 cases of tetralogy of Fallot analyzed by Abbott⁸ varied from eleven days to thirty-six years. White and Sprague have reported the case of a noted musician who lived to his sixtieth year. From the above discussion of the main factors of adaptation it would appear that the duration of life is determined by the amount of right-to-left shunt on the one hand, and the erythrocytosis on the other. The amount of the right-to-left shunt is determined by the mechanical features in the heart, namely, the size of the pulmonary valve orifice, the size of the interventricular septal defect, and the relation between the pressures developed in the right and left ventricles. Under given intraeardiac conditions the efficiency of the myocardium plays the central rôle in determining the duration of life, since upon it depend the maintenance of a requisite circulation rate and the restriction of the right-to-left shunt to within physiological limits. There are, no doubt, other changes in the blood and in the tissues which also make for maintaining normal metabolism.

Limits of Function of the Circulatory System.—From early childhood the patient was in the habit of walking at a slow pace; if he walked rapidly, he had the discomfort of breathlessness. After short but rather great exertion, like lifting a heavy box, he had to stop to recover from dyspnea in the form of rapid shallow respirations. During his stay in the hospital ward, it was noticed that the cyanosis became more intense when he changed from the upright to the recumbent posture, when he performed moderate exercise sufficient to induce dyspnea and also during the attacks described by Dr. Mills and Dr. Webster. The intensification of the cyano-

sis on change of posture may be attributed to venous congestion in the head, resulting from the effect of gravity. This, associated with exertion, indicates that the patient had, in some degree, a reserve mechanism present in normal people, namely, the ability to develop an oxygen debt, but this mechanism in our case could function only within much narrower limits than in the normal individual. The experiment performed on March 16, 1923, gives some clue to the limitations of the patient's power to provide his tissues with oxygen during exertion. Before exercise (walking up and down the ward) the arterial O_2 content was 7.32 vols. per cent and after exercise it was 5.16 vols. per cent. The O_2 content of venous blood before exercise was 3.82 vols. per cent; after, 0.66 vols. per cent. The response to exercise in this experiment exemplifies the very narrow limits of reserve within which the activities of the patient had to be maintained in order that he might be comfortable. The considerable oxygen debt of (328-241) 87 c.c. per minute was accumulated by the ordinary exertion of walking for a few minutes. The increased circulation rate associated with exercise is greatly restricted in its effectiveness by the existence of the venous arterial shunt. Moreover, it is very likely that with increase in cardiac output, the magnitude of the shunt becomes augmented both relatively and absolutely. If, to these disabilities, that of myocardial failure is added, the main compensatory mechanism lies with peripheral circulation: the margin of oxygen desaturation of the blood by the tissues is widened so that the oxygen debt rapidly accumulates in the presence of a very deficient pulmonary circulation. On one occasion oxygen was administered to the patient by the funnel method when he was at rest in bed; no effect on the cyanosis or on respiration could be detected. Richards, Riley and Hiscock⁴ observed their patient during the three days that he remained in a Barash oxygen chamber and could not find any evidence of a significant beneficial effect. "The arterial oxygen saturation rose only 5 per cent, scarcely more than the change that would occur in a normal person."

Miscellaneous Symptoms and Signs.—On his first visit to the hospital, the patient complained among other things of abdominal distress unrelated to food or exertion. Post mortem, the lesser peritoneal cavity and the Foramen of Winslow were found to be obliterated by adhesions. Whatever may have been the etiology of the inflammatory process which the adhesions represented, these findings probably explain the abdominal distress.

During the whole period of observation the urine was frequently examined and always found to contain albumin, sometimes in smaller at other times in larger quantities. Casts, red blood cells and pus cells, though always present, were never abundant. The specific gravity varied from 1.014 to 1.021. On November 28, 1924, blood urea nitrogen was 17 mg. per 100 c.c. On November 25, 1925, blood urea nitrogen was 20 mg. per 100 c.c., creatinin 1.76 mg. per cent, and the urea concentration factor

(Rabinowitch) 41. These observations on the blood are those of normal kidney function, but persistence of albuminuria with some red cells and casts are suggestive of some functional abnormality in the kidneys. Furthermore, the hypertension, observed almost invariably, would seem to point to some form of nephritis. At autopsy the kidneys showed evidence of venous congestion and parenchymatous degeneration; coupled with the normal blood findings this must exclude the possibility of nephritis. It is highly probable that the hypertension may have been due to the relatively high degree of aortic hypoplasia alone, or to some unknown factor associated with the erythrocythemia, similar to that which occurs in some cases of polycythemia rubra vera. Venous congestion in the kidneys, associated with erythrocytosis, as well as the abnormally low oxygen tension of the blood with its effect on tissue metabolism, explain the parenchymatous degeneration with persistence of albuminuria, red cells and casts.

All the observers of our case were impressed by the very pronounced degree of clubbing of the fingers and toes. Repeated x-ray examinations showed no evidence of changes in the bones of the fingers and toes, although such changes have been described. During the whole period of six years the patient was seen by different observers at different times and so no accurate statement as to whether the clubbing increased during that time can be made.

The Heart Sounds and Murmurs.—The notes made by various observers at different times revealed considerable lack of uniformity in the description of the cardiac sounds and murmurs. The unusual nature of the case and the clinical interest that the condition of the heart must have aroused in the observers make it reasonable to assume that the auscultatory signs were studied and recorded with particular care. This would tend to diminish the significance of the personal equation in comparing the records of these observations, but it must be included as one of the factors responsible for the differences found.

A systolic murmur was heard by all observers and was likewise invariably found to be loudest over the pulmonic area. The loudness of this murmur and the areas over which it was heard were variously described. In 1919 and 1923 it was described as harsh, loud, and audible all over the front and back of the chest. In 1924 a systolic murmur at the apex was recorded as faint; and, for the first time, a faint apical diastolic murmur was also mentioned: both these murmurs "are louder over the tricuspid area; they are, however, best heard in the second and third left intercostal spaces near the sternum." In 1919 the second sound was described as "loud over the aortic area and faint over the pulmonic area"; in 1924 "the second sound is loud and of equal intensity over the pulmonic and aortic areas." A systolic thrill over the pulmonic area was felt by all observers except one. In 1925 the only diastolic murmur is a "questionable presystolic murmur."

The post-mortem examination of the heart revealed at least three possible causes for a systolic murmur and two for a diastolic murmur. The congenital stenosis of the pulmonary artery, the interventricular septal defect, and the rheumatic aortic stenosis, each might be responsible for a systolic murmur. The fact that the observed murmur was loudest in the second left interspace near the sternum makes it most probable that it was due almost entirely if not entirely to the pulmonic stenosis. It appears to have been very much louder in 1919 and 1923 than in 1924 and 1925; this change may be attributed to right ventricular myocardial failure, but not without certain reservations. The systolic blood pressure was as high in 1924 when the apical systolic murmur was described as "faint," as it had been in previous years when the murmur was so loud that it was heard all over the chest. In this case the right ventricle played as great a rôle as the left ventricle, and perhaps a greater one, in maintaining systemic blood pressure, so that the blood pressure measured in the arm is indicative of the pressure in the right ventricle and of the force with which blood was projected through the stenosed pulmonary orifice. Since this force was not less in 1924 than in 1919, one may doubt whether right ventricular failure per se was responsible for the diminished loudness of the murmur. Another factor in determining the variations in loudness of the systolic murmur which deserves being mentioned is increase in peripheral resistance in the pulmonary circulation. Furthermore, if it is assumed that systolic murmurs were also produced at the slightly stenosed aortic valve and at the ventricular septal defect, diminished and increased loudness due to interference of sound waves from the three different sources may be considered as a possible explanation for the variations that were observed in the systolic murmur.

On March 17, 1923, Dr. Finley noted, "No diastolic murmur is heard," while on November 26, 1924, Dr. Howard found a diastolic murmur at the apex which was louder at the tricuspid area, and loudest over the second and third left interspace near the sternum. Between 1919 and 1924, no observer heard a diastolic murmur in spite of the fact that at autopsy a fixed pulmonic orifice was found. This may be explained in the following manner: the thinness of the pulmonary artery indicates that the difference between the pressures in the right ventricle and in the pulmonary artery during ventricular diastolic was not such as to occasion a stream of blood from the artery into the ventricle, sufficiently forceful to produce a diastolic murmur. The appearance of the diastolic murmur in 1924 must be associated with the rheumatic inflammatory deformity of the aortic valve; and this must have developed in the interval between March, 1923, and November, 1924. Judging by the blood pressure recorded a year later, shortly before his death, there could not have been much disturbance of function due to this deformity of the aortic valve.

On one occasion the spinal fluid was examined and found to issue forth at high pressure. The Noguchi, Nonne and Pandey tests for globulin were

all positive. In view of the negative Wassermann, one is led to suspect that this increase in globulin content of the spinal fluid may have been due to causes similar to those which produced the urinary findings described above. This possibility is very likely, particularly since the secretion of both fluids is dependent upon the permeability of membranes, which may have been rendered more permeable to proteins by the low oxygen saturation of the blood.

Encephalopathic Phenomena.—The pathological physiology of the cerebral symptoms cannot be discussed in the light of autopsy findings because, unfortunately, the brain was not examined. Similar cerebral phenomena have been described in cases in which the brain was examined without finding any anatomical changes to account for them. Attempts have been made to explain the mechanism of symptoms such as these on other grounds. Vaquez¹⁰ mentions the possibility that they may be attacks of Stokes-Adams syndrome. The clinical picture of unconsciousness with convulsive movements of the limbs in our case does bear some resemblance to this condition. But the normal pulse rate makes it unlikely that these attacks were initiated by ventricular asystole due to disturbance in rhythm. Various authors have, perhaps for want of a better term, called these attacks epileptiform. Our patient was a mental deficient, and this would justify serious consideration of the possibility of epilepsy in his case, but the detailed description of the attacks fails to reveal any of the stigmata of epilepsy such as tonic and clonic phases, biting of the tongue, and salivary frothing at the mouth. Dr. Ramsay, who observed and described the episode of November 30, states "attack did not suggest epileptiform attack so much as cerebral engorgement."

Abbott³ in her comprehensive work on congenital heart disease refers to "Syncopeal and Epileptiform Attacks" in cases of tetralogy of Fallot. After mentioning two cases (one of which is our own) in which there was a high degree of polycythemia, she considers the pathological physiology of these symptoms in the following terms:

"It seems probable that the great viscosity of the blood which must have existed under these conditions may have introduced some cerebral factors such as thromboses in the capillary circulation, which may have combined with the anoxemia and high unsaturation to produce this remarkable picture."

Cases of polycythemia rubra vera have been reported in which cerebral symptoms varying from headache and attacks of slight dizziness to paralyses of arms and legs occurred. In the majority of such cases in which the brain was examined, thrombosis in the cerebral vessels was found. Christian¹¹ reports ten cases, in all of which cerebral symptoms occurred. The brain was examined in four cases that showed clinical signs of permanent damage to the brain tissues. In three of these, cerebral thromboses were found; in the fourth, arteriosclerosis and cerebral softening were present.

Thromboses were present in our case: the attacks of loss of consciousness, the transitory ankle and rectus clonus, incontinence, twitching of muscles, etc., may be related to small thromboses in various parts of the brain.

The first encephalopathic symptom was headache, first mentioned in the record of the patient's symptoms in April, 1923. Two months later he began to have brief spells of dizziness without loss of consciousness, and without any symptoms suggestive of epilepsy: these occurred only when he was in the erect posture, and they gradually increased in frequency so that within six months they occurred almost daily. In December, 1924, while he was in the hospital, the first attack of loss of consciousness occurred; it is noteworthy that this began when he was seated and that there was acute pulmonary edema and flaccid paralysis during this attack. During the year following this episode there were very frequent recurrences of loss of consciousness ushered in by dizziness; these attacks came on usually when he was in the erect posture and lasted about ten minutes. He was observed in one of these attacks while in the hospital, in November, 1925; he breathed stertorously and was more deeply cyanotic than usual during this period of unconsciousness, but no blood-stained froth was observed to ooze from the mouth. The history of the nature of his death—a sudden onset of one of his attacks of unconsciousness accompanied, however, by oozing of frothy blood from the mouth—is typical of pulmonary edema due to cardiac failure, such as is met with as a medical emergency in cases of mitral stenosis. Thus there was gradually progressive increase in the severity of the encephalopathic symptoms over a period of two and a half years. During this same period the efficiency of cardiac function progressively diminished, and there appears to be a direct relationship between the severity of the cerebral symptoms and the degree of cardiac failure. This suggests another approach to the elucidation of the mechanism responsible for the encephalopathic manifestations. The headache, dizziness and transitory spells of loss of consciousness resemble the syndrome induced by anoxemia which was described by Haldane.⁷ Although our patient had a normal basal metabolism and was also able to accumulate an oxygen debt during slight exertion, the oxygen in his arterial and venous streams became rapidly diminished during exercise; the limits of his reserve were very narrow. The development of cardiac failure further impaired the efficiency of his circulation, so that one may suspect that anoxemia of the tissues occurred very readily during any physical strain. The fact that the attacks of dizziness and loss of consciousness at first appeared only when he was in the erect posture, and later even when he was lying down or sitting, and the association of some of these attacks with acute pulmonary edema, indicate the likelihood that they were initiated by transitory myocardial failure of a more or less profound degree, which led to cerebral anoxemia, the immediate cause of the symptoms.

The more severe attacks characterized by loss of consciousness, stertorous breathing, convulsive movements, constriction of the pupils followed

by marked dilatation, flaccid paralysis with loss of reflexes and incontinence of sphincters, bear a direct resemblance to the syndrome of asphyxia that may be produced experimentally in animals. Such attacks were usually accompanied by acute pulmonary edema, and it was in one of these attacks that he died.

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A METHOD FOR THE MEASUREMENT OF THE VELOCITY OF THE PULMONARY AND PERIPHERAL VENOUS BLOOD FLOW IN MAN*

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ALL methods used in the past for the measurement of the velocity of blood flow in man have consisted of the injection of a substance into a peripheral vein, and the determination of the time elapsing between the injection and the arrival of the substance at another designated point in the circulation. The time interval between injection and arrival of the fastest particle of blood through the designated portion of the circulation has been termed the circulation time for that particular pathway. The reliability of any method which employs this procedure depends primarily upon the accuracy with which the earliest traces of injected substances can be detected in the blood stream. The circulation time has been determined by: (1) The fluoresceine method of Koeh¹ in which the arrival time was indicated by the appearance of dye in the venous blood of the forearm. Technical difficulty in securing the necessary blood samples and in detecting the earliest traces of dye has made this method rather impracticable. (2) The conductivity method of Stewart² which made use of the change in electrical conductivity of the blood caused by the addition of an electrolyte. Strong sodium chloride solution was injected intravenously into animals, and its time of arrival registered through suitable electrodes and a sensitive galvanometer. Although sound in principle, and reliable in animals, its applicability in patients has not proved feasible in our experience. (3) Radium emanation has been employed successfully in estimating the velocity of blood flow.^{3, 4, 5} A small nontoxic dose of radium emanation is injected intravenously, and its arrival at one or more points in the circulation is registered by a device sensitive enough to detect the early traces of radium. This method not only permits measurement of the circulation rate in the large blood vessels but makes possible a separate estimation of the rate of blood flow in the pulmonary and peripheral circulations. In this lies its chief significance. However, despite these advantages, the expense, the technical proficiency required by the method, and its bulkiness constitute serious disadvantages and restrict its use. The fact that measurement cannot be repeated within less than three hours is also a disadvantage for certain observations. (4) A new type of method was introduced by the use of pharmacological agents such as carbon dioxide, histamine, calcium

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chloride and others for measuring the circulation rate. The arrival of the injected substances is registered by a characteristic and readily discernible effect upon some physiological function. The time interval between the injection and the bodily reaction, the reaction time,^{*} represents the circulation time from the site of injection to the responsive organ. It is essential that the signal reaction, upon which the accuracy of the reaction time largely depends, shall be objective, demand no cooperation on the part of the patient and shall occur promptly after arrival of the active agent in the reacting organ.

Because of failure to comply with one or more of these requirements the results of a number of pharmacological methods are of limited value. Bornstein⁶ attempted to measure the circulation time by the inhalation of carbon dioxide. The time interval between the inspiration of carbon dioxide and the first deep respiration was thought to be an expression of the circulation time from the capillaries of the lung to the respiratory center. Because of variations in the response to carbon dioxide in pathological conditions, Bornstein himself recognized the limited applicability of the method. Loevenhart, Schlomowitz and Seybold⁷ determined the circulation time in animals by injecting sodium cyanide intravenously. The resulting stimulation of respiration was used as an indication of the arrival of cyanide in the respiratory center. Although the circulation time by this method compared favorably with those obtained by ferrocyanide, hexamethylene and lithium chloride in the rabbit and dog, no application of it was made in man. The histamine method⁸ depends upon the intense flush of face and neck caused by the arrival of histamine in the small blood vessels of the skin. A salty or metallic taste occurs simultaneously with the onset of the flush and serves as a verification of the arrival time of histamine. Headache following its use and its failure to produce an objective reaction in severe anemia and in dark-colored races limit its usefulness. In 1930 Kahler⁹ employed calcium chloride for estimating the rate of blood flow in various parts of the body. He injected calcium chloride intravenously and made use of the sensation of heat which followed its course throughout the body in estimating the circulation time to the head and neck, hands, feet and buttocks. Although the results reported by Kahler are in fair agreement with the circulation time obtained with other reliable methods, the method must be limited in application because of the entirely subjective nature of the reaction. More recently Winternitz, Deutsch and Brüll¹⁰ used decholin, a preparation of dihydrochloric acid which produces a sudden intensely bitter taste upon arrival in the mouth. This method, again, is subjective, dependent upon the intelligence and cooperation of the subject and, therefore, cannot be trustworthy in many pathological conditions.

^{*}The term reaction time refers to the time interval between injection and reaction. It should not be confused with the term reaction time proper which is the period required for reaction to occur after arrival of the pharmacological agent in the reacting organ.

Each of the different methods for estimating the velocity of blood flow offers certain advantages, depending upon the nature of the inquiry; and each possesses limitations which must be considered in the selection of a method.

THE PROBLEM

In order to study sudden changes in the circulation in certain diseases a reliable method was needed for measuring at frequent intervals the rate of blood flow in man which could be used at the bedside with little delay, and preferably by one observer. None of the available methods met with these requirements. The conductivity method of Stewart,² as well as the modifications of Meldolesi¹¹ and Koch,¹² proved unsuitable. We were, therefore, forced to find a chemical substance which, through its pharmacological properties, might be satisfactory.

A chemical substance suitable for measurement of the velocity of blood flow in man should fulfill the following requirements: (1) It should be nontoxic in the dose employed. (2) It should not influence the velocity of blood flow until the signal reaction has occurred. (3) The substance and its effect on the body should be rapidly inactivated so that measurements may be repeated after short intervals of time. (4) The signal reaction of primary importance in the method must be objective and readily discernible in both normal and pathological conditions. It should be suitable for graphic registration. The reaction time proper of the substance after arrival in the reactive organ should be a negligibly small fraction of the entire reaction time which consists of circulation time plus reaction time proper.

The pharmacological studies of Loevenhart and his coworkers¹³ on the effect of sodium cyanide suggested this substance as a suitable agent for measurement of the velocity of blood flow in man. They administered sodium cyanide intravenously to animals and man and found it to be a safe and effective stimulant of respiration when given in proper dosage. A latent period invariably occurred between the injection of cyanide and increased respiration, which suggested to them its use for measuring the circulation time of the blood. Although experiments in animals later demonstrated its exceptional qualification for this rôle,⁷ cyanide was not used for measurement of the circulation time in man as far as can be ascertained.

The cyanide radical, although usually regarded as highly toxic, occurs normally in certain plants¹⁴ and even in the animal body. Cyanide in the form of thiocyanate is a normal constituent of human saliva,¹⁵ urine,¹⁶ and gastric juice.¹⁷

Cyanide stimulates all of the medullary centers, but the most striking effect is upon respiration. Small doses cause an increase in the rate and amplitude of respiration, whereas toxic doses produce a fleeting stimulation, followed rapidly by shallow irregular breathing, and finally by a paralysis of respiration and death. According to Loevenhart¹³ the respiratory stimulating dose of sodium cyanide in man, when injected

rapidly into the vein, is 3 to 5 mg., approximately 0.04 to 0.07 mg. per kg. of body weight; whereas the fatal dose of injected sodium cyanide in both animals and man was estimated to be about twenty times the respiratory stimulating dose. The toxicity of sodium cyanide is considerably lower than that of several of the glucosides and alkaloids employed in clinical medicine.¹⁴ Cumulative effects do not readily occur from the therapeutic administration of cyanide because of its rapid inactivation in the body, which progresses, according to Loevenhart, at the rate of 1.5 to 2 mg. per minute in man. It is converted in part into relatively innocuous sulphur compounds, and in part into less closely related nitrogenous compounds. Excretion occurs as hydrocyanic acid on the breath and as cyanide and sulphocyanide in the urine.¹⁸ These data on the pharmacology of the cyanide group clearly indicate that sodium cyanide can be safely administered to man intravenously in amounts to cause a distinct stimulation of respiration, and that this can be repeated after short intervals of time.

PLAN OF INVESTIGATION

In order to find out, in the first place, whether sodium cyanide could be safely administered to man in amounts adequate to cause distinct stimulation of respiration, it was administered intravenously in varying amounts to a large number of volunteer subjects, and its effect on respiration and circulation was observed.

In order to ascertain whether the reaction time of cyanide would be an accurate measure of the true circulation time and whether a practical application could be made clinically, the following observations were made. The reaction time of cyanide in normal subjects was compared with the circulation time obtained by the radium emanation and histamine methods. The constancy of the reaction time with varying doses of cyanide was investigated. Repeated estimations were made at short intervals to ascertain whether frequent determinations of the cyanide reaction time were feasible. For comparison of the results obtained by two methods under identical conditions, estimations of the circulation time by both the cyanide and the histamine methods were performed in the same individual. For a more precise evaluation, simultaneous determinations of the cyanide reaction time and glucose circulation time were made.

OBSERVATIONS ON THE EFFECT OF SODIUM CYANIDE IN MAN

The Dosage of Cyanide.—We found, as anticipated, that the greater the concentration of sodium cyanide and the smaller the volume of solution injected the more abrupt and intense was the respiratory stimulation. A 2 per cent aqueous solution of sodium cyanide (C. P. Merek), which permitted the rapid injection of an effective dose of cyanide in small volume without significant alteration in blood volume or velocity of blood flow, proved the most suitable concentration. The injections were made

rapidly from a graduated 1 c.c. Luer syringe into a large peripheral vein, usually the antecubital vein of the forearm, of resting subjects whose cooperation had been gained previously. Initial ineffective amounts of cyanide were gradually increased until a marked respiratory response was obtained. Later, however, only doses within the effective range for respiratory stimulation were administered.

The intensity of respiratory stimulation was, in general, proportional to the quantity of cyanide injected. Small amounts, such as 2 to 4 mg., caused indefinite respiratory reactions, whereas large doses, as 10 to 20 mg., produced intense dyspnea, labored breathing and tachycardia. The quantity of cyanide required to cause a moderately intense or optimal respiratory response varied considerably but was roughly proportional to body weight. In 35 normal* subjects the optimal dose of cyanide, when injected into the *antecubital vein* of the forearm, ranged from 5 mg. to 10 mg. corresponding to 0.25 to 0.5 c.c. of 2 per cent aqueous solution of sodium cyanide, or 0.07 mg. to 0.19 mg. per kg. of body weight. The average optimal dose was 7 mg. or 0.35 c.c. of 2 per cent solution, or 0.11 mg. per kg. of body weight.

The optimal dosage of sodium cyanide required for *jugular injection* was approximately two-thirds of the antecubital dosage. It varied from 3 to 6 mg., corresponding to 0.15 to 0.3 c.c. of 2 per cent solution of sodium cyanide, or 0.05 to 0.1 mg. per kg., with an average value of 4 mg., equivalent to 0.2 c.c. of 2 per cent solution, or 0.066 mg. per kg.

The quantity of cyanide required to cause an adequate respiratory reaction, however, may in certain instances differ by 100 per cent from the calculated dose. This is particularly true in pathological conditions with dyspnea in which smaller amounts of cyanide must be administered. The nature of the respiratory response and cyanide dosage in disease will be discussed in a later publication.

The range of safe effective dosage in normal subjects was found to be wide. Three times the optimal dosage of cyanide was administered without untoward reactions.

The Effect of Cyanide on Respiration.—The optimal intensity of respiratory response to cyanide was characterized by a sudden abrupt onset which interrupted the existing phase of respiration, rapid progression to maximal intensity of respiration, and prompt return to normal breathing. The amplitude of respiration invariably increased several fold, in striking contrast to the rate of respiration which was but little accelerated and occasionally slowed. The duration of increased respiration varied from 15 to 30 seconds in normal subjects, usually about 20 seconds. No unpleasant subjective responses accompanied optimal respiratory stimulation in normal subjects. The cyanide reactions caused respiratory discomfort only when maximal ventilatory responses were produced.

*The term normal refers to normal adults without disease, and to convalescent hospital patients who presented no evidence of circulatory, respiratory, hemic or metabolic disease at the time of observation.

The Effect of Cyanide on the Circulation.—Coincident with, or immediately after, the onset of increased respiration an acceleration of the heart rate of 10 to 15 beats per minute generally occurred which persisted from three to five minutes. Rarely the heart rate decreased.

Inactivation of Cyanide.—Precise observations on the rate of cyanide inactivation in man were not made. The observations, however, on the persistence of the effect of cyanide on respiration and circulation indicate that the effect is transient, lasting only a few minutes, and are in agreement with the rate of inactivation of sodium cyanide in man observed by Loevenhart.¹³

No accidents or undesirable systemic reactions have occurred in our experience with cyanide administration. Local pain of short duration has followed perivascular infiltration with cyanide, but in no instance has thrombosis or necrosis occurred. We believe that sodium cyanide can be administered to man within a wide range of dosage and cause clear-cut stimulation of respiration without unpleasant side effects or serious consequences.

THE REACTION TIME OF CYANIDE IN NORMAL SUBJECTS

All measurements of the cyanide reaction time were made in subjects who had been resting in the recumbent position for twenty minutes or until the heart rate and blood pressure were constant. For accurate results it was found essential to avoid excitement which was liable to follow venepuncture. To minimize this effect the sites of cyanide injection were anesthetized with novocaine. This is particularly important in sensitive areas such as the foot and neck. Venous stasis, when required for venepuncture, was released promptly, and a time interval allowed for adequate restoration of normal venous blood flow before injection. The arm in which the injection was made, rested at the level of the right auricle. Optimal amounts of sodium cyanide in 2 per cent solution, sufficient to produce unequivocal signal reactions, were then injected rapidly intravenously so that the duration of injection rarely exceeded 0.5 second.

An objective measure of the reaction time of cyanide was accomplished by the combined use of kymograph, pneumograph, signal magnet and time marker for automatic registration of the time of injection and the onset of the respiratory reaction. An example of such graphic registration of the reaction time is shown in Fig. 1. As subsequent observations showed that the reaction time measured with a stopwatch coincided with that obtained with graphic registration, the former simpler method was adopted as adequate in routine determinations.

To secure separate measurements of the pulmonary and peripheral venous circulation time two or more sites for subsequent injections were employed: (a) A peripheral vein of the forearm or the foot, depending upon the peripheral circulation to be studied. For reasons discussed subsequently, the circulation times from these sites of injection were called

TABLE I
THE ARM-TO-CAROTID REACTION TIME OF CYANIDE IN NORMAL SUBJECTS

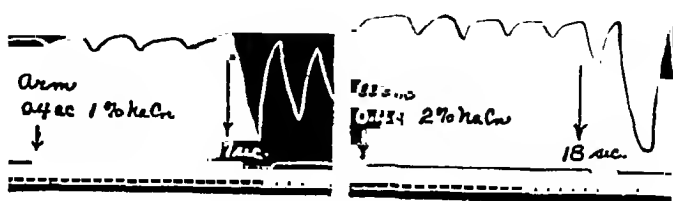
NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		VITAL CAPACITY		SODIUM CYANIDE OPTIMAL DOSAGE		NUMBER OF DETERMI- NATIONS	RE- ACTION TIME	MAXIMAL VARI- ATION IN REAC- TION TIME	DIAGNOSIS
			SYSTOLIC	DIASTOLIC	OB- SERVED	PER SQ. M.	Mg.	Mg./Kg.				
		PER MIN.	MM. HG	MM. HG	C.C.	C.C.				SEC.	SEC.	
R. F.	15	96	110	60	4200	2530	5	0.08	2	9	0	Appendectomy, convalescent
W. D.	26	74	100	60	4600	-	6	0.08	2	10	0	Upper respiratory infection, con- valescent
W. N.	18	94	120	80	4450	2550	6	0.07	2	12	1	Peptic ulcer, convalescent
D. C.	17	72	125	85	4300	2400	6	0.09	3	13	0	Upper respiratory infection, con- valescent
F. F.	17	72	110	45	-	-	6	0.11	3	13	0	Neurosis
K. M.	26	100	120	80	5200	2770	8	0.11	2	13	1	No disease
R. R.	27	88	115	60	4100	2260	10	0.14	4	13	3	Peptic ulcer, convalescent
Q. V.	48	80	100	55	4800	2550	6	0.08	3	13	2	Amputation of leg, convalescent
J. R.	31	82	120	80	4200	2470	8	0.13	4	14	1	Neurosis
H. D.	35	60	135	85	4550	2400	8	0.12	2	14	2	Neurosis
M. C.	45	84	120	75	3800	2090	8	0.11	2	14	1	No disease
H. S.	46	70	120	80	3800	2140	6	0.09	2	14	0	Pneumonia, convalescent
E. C.	50	84	125	80	3500	1900	6	0.13	2	14	1	Peptic ulcer, convalescent
W. T.	21	72	110	70	4500	2510	6	0.09	1	15	-	Atrophic arthritis, convalescent
M. B.	24	96	120	75	4500	2840	6	0.11	2	15	0	No disease
C. D.	25	82	110	65	4300	2330	5	0.08	2	15	0	Amputation of leg, convalescent
J. M.	48	84	155	85	3600	2130	6	0.10	1	15	0	Infectious arthritis, convalescent
J. P.	17	66	90	55	4200	2320	8	0.12	3	16	1	Tonsillitis, convalescent
J. K.	21	76	130	75	3900	2280	8	0.13	2	16	2	Vincent's angina, convalescent

TABLE I—CONTINUED

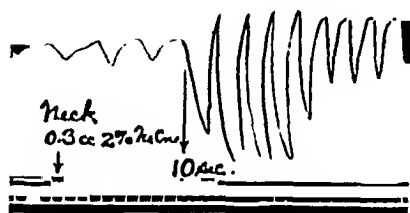
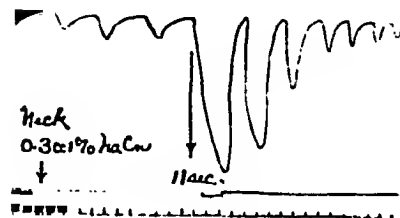
NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		VITAL CAPACITY		SODIUM CYANIDE OPTIMAL DOSAGE		NUMBER OF DETERMI- NATIONS	RE- ACTION TIME	MAXIMAL VARI- ATION IN REAC- TION TIME	DIAGNOSIS
			SYSTOLIC	DIASTOLIC	OB- SERVED	PER SQ. M.	MG.	MG./KG.				
F. W.	32	PER MIN. 76	115	MM. HG 75	C.C. 4800	C.C. 2640	6	0.09	1	SEC. 16	SEC. —	Upper respiratory infection, con- valescent
A. K.	42	60	140	80	—	—	6	0.11	2	16	2	Neurosis
J. L.	44	78	105	75	—	—	6	0.13	3	16	1	Diabetes mellitus, mild
S. G.	17	72	110	65	4500	2340	10	0.14	2	17	0	Neurosis
P. M.	25	74	115	60	—	—	6	0.09	5	17	1	Cervical adenitis, convalescent
E. L.	28	88	125	80	—	—	8	0.12	2	17	2	No disease
M. T.	37	80	115	70	3200	2040	10	0.19	2	17	0	Tonsillitis, convalescent
R. D.	60	68	120	70	3100	1980	6	0.12	4	17	2	Hypertrophic arthritis, improved
O. T.	25	76	125	60	4000	2270	6	0.10	2	18	2	No disease
J. R.	25	66	120	65	—	—	5	0.08	2	18	1	Upper respiratory infection, con- valescent
H. J.	27	76	120	80	6200	3000	10	0.14	1	18	—	No disease
C. D.	25	86	105	65	—	—	6	0.12	2	19	1	Pleurisy, convalescent
W. S.	31	84	120	85	5200	2610	7	0.11	2	20	2	No disease
R. G.	32	80	130	85	5800	3100	6	0.09	2	20	1	No disease
J. S.	41	84	145	85	3300	1990	10	0.17	1	20	—	Pneumonia, convalescent
J. D.	36	78	110	75	4300	2390	8	0.12	5	21	4	Burn, convalescent
Average	31	79	119	72	4320	2400	7	0.11	2	15.6	1	

the arm-to-carotid or foot-to-carotid circulation time. (b) The external jugular vein. This gave a measure of the crude pulmonary circulation time but included a short peripheral venous pathway. By difference the venous velocity index was derived, thus providing a practical estimation

I



II



III

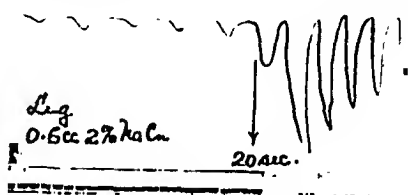
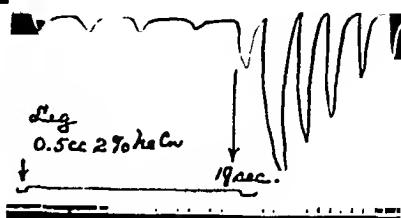


Fig. 1.—Graphic registration of the cyanide circulation time in subject P. M. I Arm-to-carotid circulation time. II Crude pulmonary circulation time. III Foot-to-carotid circulation time.

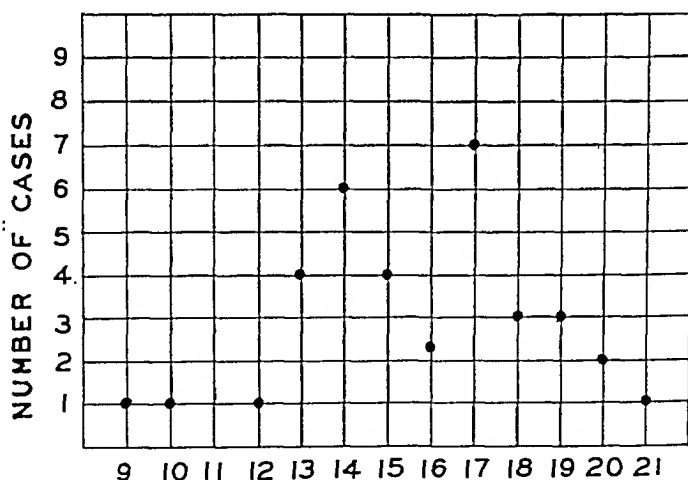


Fig. 2.—The arm-to-carotid circulation time in seconds, in 35 normal subjects.

of the velocity of venous blood flow, but not an exact measure of the circulation time from the point of injection to the right side of the heart.

The arm-to-carotid circulation time (antecubital injection) was determined in 35 normal subjects. In 21 of the 35 subjects the crude pulmonary circulation time (jugular injection) was also estimated. The arm-to-ca-

rotid reaction times and other observations are presented in Table I. The cyanide reaction time varied between 9 and 21 seconds; the average reaction time was 15.6 seconds. These values are in harmony with those obtained by the radium emanation method⁴ in normal subjects in which the average arm-to-arm time was 17.5 seconds. It is of interest that the distribution of the cyanide reaction times (Fig. 2) is also similar to that obtained by the radium emanation method. The arm-to-carotid reaction time, the crude pulmonary circulation time, and the peripheral arm venous velocity index together with other observations are presented in Table II. The average heart rate, blood pressure, and vital capacity support the contention that the findings on the velocity of blood flow were measured under adequately normal conditions. The average crude pulmonary circulation time was 10.6 seconds, ranging from 7 to 14 seconds. The distribution curve is shown in Fig. 3. Here again, both average and extreme values and

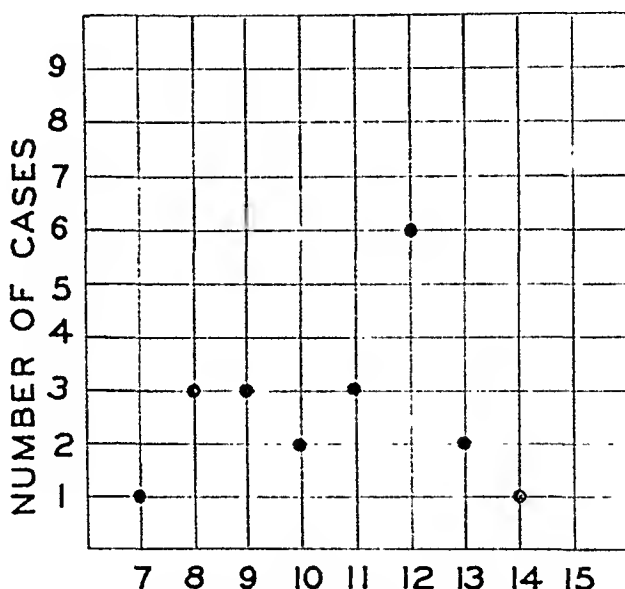


Fig. 3.—Crude pulmonary circulation time in seconds in 21 normal subjects.

character of distribution are in agreement with the crude pulmonary circulation times obtained by the radium emanation method.⁵

The index of venous velocity, which is derived by subtracting the crude pulmonary circulation time from the arm-to-carotid circulation time, expresses the circulation time for approximately three-quarters of the venous pathway from antecubital vein to heart, not the entire arm-to-heart circulation time. The venous circulation time, according to observations with the radium emanation method, is more variable and of less significance than the pulmonary circulation time. The same is true in this study. The individual measurements (Table II) ranged from 1 to 9 seconds. The average venous velocity index for the 21 subjects was 4.5 seconds. These results are in accord with those of the radium emanation method in which the average arm-to-heart circulation time was 6.6 seconds. If allowance be made for the shorter pathway represented by the venous velocity index, the results obtained with these methods become almost identical.

TABLE II
THE ARM-TO-CAROTID AND CRUDE PULMONARY REACTION TIMES IN NORMAL SUBJECTS

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		VITAL CAPACITY		SODIUM CYANIDE OPTIMAL DOSAGE		REACTION TIME		VENOUS VELOCITY INDEX	DIAGNOSIS
			SYSTOLIC	DIASTOLIC	OBSERVED	PER SQ. M.	ARM TO CAROTID	CRUDE PULMONARY	ARM TO CAROTID	CRUDE PULMONARY		
		PER MIN.	MM. HG	MM. HG	C.C.	C.C.	MG./KG.	MG./KG.	SEC.	SEC.	SEC.	
W. N.	18	94	120	80	4450	2550	0.07	0.05	12	7	5	Peptic ulcer, convalescent
F. F.	17	72	110	45	-	-	0.11	0.07	13	8	5	Neurosis
J. P.	17	66	90	55	4200	2320	0.12	0.09	16	9	7	Tonsillitis, convalescent
J. K.	21	76	130	75	3900	2280	0.13	0.08	16	9	7	Vincent's angina, convalescent
O. T.	25	76	125	60	4000	2270	0.10	0.07	18	9	9	No disease
W. D.	26	74	100	60	4600	-	0.08	0.06	10	9	1	Upper respiratory infection, convalescent
M. C.	45	84	120	75	3800	2090	0.11	0.06	14	9	5	No disease
D. C.	17	72	125	85	4300	2400	0.09	0.06	13	10	3	Upper respiratory infection, convalescent
E. C.	50	84	125	80	3500	1900	0.13	0.07	14	10	4	Peptic ulcer, convalescent
W. T.	21	72	110	70	4500	2510	0.09	0.06	15	11	4	Atrophic arthritis, convalescent
P. M.	25	74	115	60	-	-	0.09	0.05	17	11	7	Cervical adenitis, convalescent
H. S.	46	70	120	80	3800	2140	0.09	0.05	14	11	3	Pneumonia, convalescent
F. W.	32	76	115	75	4800	2640	0.09	0.06	16	11	5	Upper respiratory infection, convalescent
S. G.	17	72	110	65	4500	2340	0.14	0.08	17	12	5	Neurosis
C. D.	25	82	110	65	4300	2330	0.08	0.05	15	12	3	Amputation of leg, convalescent
H. D.	35	63	135	85	4550	2460	0.12	0.08	14	12	2	Neurosis
J. M.	48	84	155	85	3600	2130	0.10	0.07	15	12	3	Atrophic arthritis, convalescent
J. R.	31	82	120	80	4200	2470	0.13	0.10	14	12	2	Neurosis
R. G.	32	80	130	85	5800	3100	0.09	0.05	20	13	7	No disease
R. D.	60	68	120	70	3100	1980	0.12	0.06	17	13	4	Chronic arthritis, improved
J. R.	25	66	120	65	-	-	0.08	0.07	18	14	4	Upper respiratory infection, convalescent
Average	30	75	119	71	4220	2335	0.103	0.066	15.1	10.6	4.5	

TABLE III
VENOUS CIRCULATION TIME OF ARM AND LEG

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		SODIUM CYANIDE PER KG.			CYANIDE REACTION TIME			VENOUS VELOCITY INDEX		DIAGNOSIS
			SYSTOLIC	DIASTOLIC	ARM	FOOT	NECK	ARM TO CAROTID	FOOT TO CAROTID	CRUDE PULMONARY	ARM	LEG	
		PER MIN.	MM. HG	MM. HG	MG.	MG.	MG.	SEC.	SEC.	SEC.	SEC.	SEC.	
R. D.	60	68	120	70	0.12	0.16	0.06	17	29	13	4	16	Hypertrophic arthritis
E. C.	50	84	125	80	0.13	0.21	0.07	14	27	10	4	17	Peptic ulcer
J. Mc.	67	96	150	80	0.06	0.10	0.04	19	24	14	5	10	Arteriosclerosis
Q. F.	49	80	100	65	0.09	0.17	0.07	17	20	11	6	9	Neurosis
T. K.	48	72	140	85	0.10	0.16	0.07	18	29	12	6	17	Peptic ulcer
P. M.	25	74	115	60	0.09	0.15	0.05	17	19	10	7	9	Adenitis
R. G.	32	80	130	85	0.09	0.18	0.05	20	25	13	7	12	Normal
J. K.	45	72	130	70	0.10	0.17	0.07	22	30	13	9	17	Inactive pulmonary tuberculosis
A. R.	57	66	150	70	0.08	0.16	0.06	22	34	14	8	20	Arteriosclerosis
F. E.	62	72	160	100	0.09	0.16	0.08	24	40	16	8	24	Lead poisoning, convalescent
Average					0.09	0.16	0.06	19.0	27.7	12.6	6.4	15.1	

This method for estimating the velocity of venous blood flow can be employed in other regions of the body. To demonstrate the feasibility of this application of the cyanide method we have estimated the venous circulation time in both arm and leg in 10 individuals.

The venous circulation time of the arm was determined in the usual manner. The venous circulation time of the leg was obtained by injection into a dorsal vein of the foot. The dosage of cyanide required for the foot injection was found to be approximately 1.5 times the amount effective when injected in the arm. This difference in dosage is distinctly less than that with the histamine method. The leg circulation time was considerably longer than the arm circulation time (Table III), as shown by the average value of 15.1 seconds and 6.4 seconds, respectively. This difference is explained by the longer venous pathway from the foot to the heart.

By estimating the reaction time at different levels in the same venous pathway the circulation time for the designated portion can be ascertained. Such a differential estimate of the velocity of blood flow in various portions of the venous system may be of aid in a number of diagnostic problems. This procedure was undertaken in one subject who had many varicose leg veins. Consecutive injections were made into a dorsal vein of the foot, the great saphenous vein at the knee and the femoral vein at the groin. The reaction times were 46, 28, and 12 seconds, respectively.

A Comparison of the Results Obtained by the Radium, Histamine and Cyanide Methods.—To confirm the reliability of the cyanide method we have compared our results with those of the histamine as well as the radium emanation methods. The histamine method affords a measure of the circulation time from the arm to the small blood vessels of the face and brain; whereas the radium method measures the circulation time from the antecubital vein of one arm to the large brachial artery of the opposite arm, a pathway more clearly defined and less subject to variation. The pathways, therefore, differ fundamentally in character and in length. This is reflected in the difference in circulation time obtained with the two methods. The histamine reaction time, because of the peripheral location of its site of reaction, is consistently longer than the arm-to-arm circulation time of the radium method.

The results obtained with each method and the vascular pathways used are presented in Table IV. There is practical agreement throughout between the results obtained with the radium and cyanide methods, indicating that in normal subjects the reaction time to cyanide is a trustworthy measure of the circulation time. The longer average histamine reaction time of 23 seconds, however, contrasts strikingly with the cyanide reaction time of 15.6 seconds. Although a somewhat shorter reaction time had been anticipated because of the possibly greater rapidity of action of cyanide, such divergence between the results obtained with methods employing pathways regarded as essentially the same required explanation.

To verify the existence of a significant difference between the reaction time obtained with the two pharmacological methods we estimated the reaction time of both cyanide and histamine in 8 subjects under identical conditions but not simultaneously. These observations, which are recorded in Table V, clearly show that in the same individual the cyanide reaction time was, without exception, shorter than that of histamine. The difference varied from 4 to 9 seconds with an average difference of 6.5 seconds, which is of sufficient constancy and magnitude to indicate an essential difference in the vascular site of reaction.

TABLE IV

COMPARISON OF CIRCULATION TIMES IN NORMAL SUBJECTS DETERMINED BY THE RADIUM EMANATION, CYANIDE AND HISTAMINE METHODS

VASCULAR PATHWAY	RADIUM EMANATION METHOD		CYANIDE METHOD		HISTAMINE METHOD	
	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE
	SEC.	SEC.	SEC.	SEC.	SEC.	SEC.
Arm to heart	6.6	2-14				
Arm peripheral venous			4.5	1-9		
Crude pulmonary	10.8	5-17	10.6	7-14		
Arm to arm	17.5	14-24				
Arm to carotid			15.6	9-21		
Arm to face					23	13-30

TABLE V

COMPARISON OF HISTAMINE AND CYANIDE CIRCULATION TIMES IN THE SAME INDIVIDUAL

NAME	AGE	DIAGNOSIS	HISTAMINE REACTION TIME ARM TO FACE	CYANIDE REACTION TIME ARM TO CAROTID	DIFFERENCE
	YEARS		SEC.	SEC.	SEC.
C. D.	25	Amputation of leg	22	15	-7
R. R.	27	Neurosis	19	13	-6
M. T.	37	Tonsillitis	23	17	-6
Q. V.	48	Amputation of leg	18	12	-6
E. C.	50	Peptic ulcer	19	13	-6
J. M.	56	Cholecystitis	28	20	-8
R. D.	60	Arthritis	26	17	-9
P. R.	57	Arteriosclerosis	18	14	-4
Average			21.6	15.1	-6.5

Histamine is known to exert its dilator action directly upon the minute vessels of the skin and the brain. The flush is due mainly to its primary action on the small veins. The reaction time of histamine, therefore, is the time required for the blood to flow to the subpapillary venules rather than to a more proximal point of the large arteries, as is the case with the radium

method. We have, previously, attributed the prolonged reaction time of the histamine method to a considerable slowing of blood flow in the smaller vessels. Hering¹⁹ estimated the capillary circulation time to be 5 seconds; according to Koch's observations¹ the capillary time would correspond to 8 seconds in man. Similarly, in this laboratory, study of capillaries by direct observation showed the rate of blood flow to be slow.

In contrast to histamine our knowledge of the site of action of cyanide in man is meager. The increase in respiration caused by its administration has been assumed to be due to the direct action of cyanide on the respiratory center. This would require that cyanide must also be delayed in arriving at the respiratory center, because of the similarity in blood supply and circulation time to the skin of the face and the brain.⁸ Thus, unless there is a considerable difference in the rapidity of action of these two substances after their arrival in the capillaries of the brain, their reaction time should be in close agreement. Since the large difference of 6.5 seconds between the two methods cannot be ascribed to a more rapid action of cyanide after its arrival, it must be explained by a shorter pathway and circulation time of the blood to the site of cyanide action. Such a postulation would exclude the respiratory center as the site of cyanide stimulation of respiration.

The recent investigations of Heymans, Bouckaert and Dantrebande,²⁰ confirmed by Owen and Gesell,²¹ have thrown new light on the mechanism of the action of cyanide on the respiration. By denervation experiments in animals these investigators demonstrated conclusively that sodium cyanide exerts its action predominantly upon the carotid sinus, a portion of the common carotid artery near the bifurcation and in contact with the respiratory center through afferent nerves; and that sodium cyanide has little or no effect directly upon the respiratory center. They further observed that the stimulation of respiration occurred instantaneously after the injection of cyanide into the common carotid artery. According to this evidence the reaction time to cyanide is the time required for blood to flow to the carotid sinus of the carotid artery. This provides a rational explanation for the shorter reaction time of the cyanide method, and also its correspondence with the results obtained with the radium emanation method.

Since the action of cyanide on the carotid sinus of man has not been demonstrated, we resorted to indirect methods to throw additional light on the mechanism of cyanide action in man.

In order to ascertain whether or not the cyanide reaction time corresponds to the time required for the blood flow to reach the carotid artery, the cyanide reaction time and the actual circulation time were determined simultaneously in 7 individuals. An adequate amount of sodium cyanide, dissolved in 5 c.c. of a 50 per cent glucose solution was injected rapidly into the antecubital vein of the arm and the circulation times of both the cyanide and the glucose were determined. The usual method of register-

ing the reaction time of cyanide was used. The circulation time of glucose was determined by its appearance in the arterial blood, as shown in blood samples obtained from the femoral artery at known intervals of time. In each case satisfactory estimations of both circulation times were obtained similar to those reported for subject M. I. in Fig. 4. The results for the

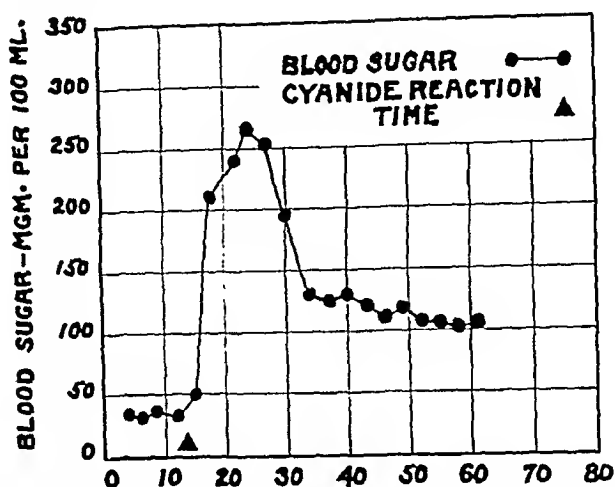


Fig. 4.—Simultaneous determinations of the arm-to-femoral glucose circulation time and arm-to-carotid cyanide reaction time in seconds, in subject M. I.

TABLE VI

COMPARISON OF CIRCULATION TIMES DETERMINED SIMULTANEOUSLY BY THE GLUCOSE AND CYANIDE METHODS

NUM- BER	NAME	AGE	DIAGNOSIS	GLUCOSE CIRCULATION TIME ARM TO FEMORAL	CYANIDE CIRCULATION TIME ARM TO CAROTID	DIFFER- ENCE
				SEC.	SEC.	SEC.
1	H. S.	46	Pneumonia, conva- lescent	11	13	+2
2	M. R.	49	Arteriosclerosis	14	14	0
3	M. I.	49	Arteriosclerosis, hypertensive heart disease	15	13	-2
4	F. P.	62	Hypertensive heart disease	19	17	-2
5	R. M.	62	Hypertensive heart disease	25	23	-2
6	P. F.	68	Arteriosclerotic heart disease decompensation	26	24	-2
7	J. F.	49	Luetic heart disease decompensation	28	25	-3
			Average	19.7	18.4	-1.3

seven subjects are summarized in Table VI, and show remarkably close agreement of the reaction time of cyanide and the circulation time of the blood to the femoral artery. In the majority of subjects the circulation time of the blood to the femoral artery was slightly longer than the cyanide reaction time. The average prolongation of 1.3 seconds corresponds closely

to the longer arterial circulation pathway of the blood to the femoral artery than to the carotid artery. This difference of 1.3 seconds is the more significant, as opening of the femoral artery should theoretically increase the velocity of blood flow in that vascular area. The close agreement then between the reaction time of cyanide and the circulation time to the femoral artery we accept as substantial, although indirect, evidence that in man as well as in animals sodium cyanide acts upon the carotid sinus. Thus the cyanide reaction time measures the velocity of blood flow between an arbitrarily chosen vascular area and a large artery, as does the radium emanation method. It may also be concluded from the close agreement of reaction time and circulation time in man, as well as by animal experiment,²⁰ that cyanide provokes an immediate increase of respiration upon arrival in the carotid sinus; and that the time required for cyanide to act after arrival must be a negligibly small part of the total reaction time. This state of affairs makes sodium cyanide a particularly adaptable substance for the measurement of the velocity of blood flow.

The Effect of Dosage on the Reaction Time.—A delay in the occurrence of the respiratory response to cyanide was observed whenever only slightly effective doses of cyanide were used. To find out whether the reaction time of cyanide varied with the dosage, it was administered in amounts to cause varying degrees of response, and the reaction time to each was determined. A suboptimal response was usually associated with a prolongation of reaction time varying from 3 to 10 seconds; whereas, with all doses sufficient to call forth an abrupt, definite stimulation of respiration, the reaction

TABLE VII

THE EFFECT OF DOSAGE ON THE REACTION TIME OF CYANIDE (SUBJECT R. G.)

TIME OF DETERMINATION	HEART RATE	SODIUM CYANIDE INJECTED	REACTION TIME	INTENSITY OF REACTION
	PER MIN.	MG.	SEC.	
1:36 P.M.	76	2	...	0
1:40	76	4	...	0
1:46	76	5	22	1+
1:51	78	6	18	2+
2:06	76	7	17	2+
2:15	78	8	16.5	3+
2:22	76	9	16	3+
2:32	76	10	16	4+
2:46	78	12	16	4+

times were remarkably constant. The results obtained in one of numerous experiments are presented in Table VII. The dose of 5 mg. (0.07 mg. per kg.) produced only a mild reaction occurring 22 seconds after injection; whereas 7 mg. caused a satisfactory reaction with a reaction time of 17 seconds which was not altered significantly with larger doses, although the intensity of reaction was increased. Thus, the reaction time of cyanide is

significantly affected by the dosage only when amounts are employed that do not give clear-cut, sudden respiratory reactions.

Repeated Estimations of the Reaction Time to Cyanide.—In order to ascertain beyond doubt the feasibility of employing the cyanide method at frequent intervals, repeated estimations were made of the reaction time of cyanide at close intervals of time in eight normal subjects. In each instance an optimal quantity was administered, and the heart rate was permitted to return to normal before subsequent injections were given. The number of determinations, as indicated in Table VIII, varied from 3 to 8 for each subject, and the time intervals between injections from 4 to 19 minutes. The reaction times in the same individual agreed as a rule within 2 seconds. In subjects J. D., R. R., and J. R. the maximal difference of 3

TABLE VIII
REPEATED DETERMINATIONS OF THE REACTION TIME OF CYANIDE

NAME	AGE	DIAGNOSIS	HEART RATE	NUMBER OF DETERMINATIONS	AVERAGE TIME INTERVAL BETWEEN DETERMINATIONS	RANGE OF REACTION TIME
			PER MIN.		MIN.	SEC.
J. P.	17	Tonsillitis, convalescent	66	3	10	15-16
Q. V.	48	Amputation of leg	80	3	4	12-14
J. L.	44	Diabetes	78	3	8	16-17
R. D.	60	Arthritis	68	4	6	16-18
P. M.	25	Adenitis, convalescent	70	5	12	17-18
J. D.	36	Burn, convalescent	78	5	13	18-22
R. R.	27	Peptic ulcer	88	7	19	9-13
J. R.	31	Neurosis	82	8	11	13-16

to 4 seconds was associated with restlessness which occurred after frequent repetitions of the test. The time intervals represented here do not express the shortest interval possible between estimations, for no attempt was made to estimate this aspect precisely. We have, however, observed frequently that the estimation of the cyanide reaction time can be repeated satisfactorily at 3 to 5 minute intervals provided that the heart rate has returned to normal before subsequent estimations are made.

DISCUSSION

In outlining the problem of this investigation it was stated that the cyanide method, in order to be suitable for measuring the velocity of blood flow in man, should fulfill certain prerequisites. In the light of our experience cyanide fulfills these requirements in the following manner:

In repeated observations no serious effects followed its administration intravenously. A wide range of effective but safe dosage of sodium cyanide exists, sufficiently removed from the dangerous dose to warrant its use in man.

Cyanide does not influence the velocity of blood flow during the first circulation of the blood after injection until the respiratory response has occurred. This is supported by the absence of any change in the heart rate, pulse or arterial blood pressure prior to the occurrence of increased respiration.

The inactivation of cyanide and the disappearance of its effect progress rapidly in the body. The more pronounced stimulation of respiration is fleeting, lasting for only several seconds, whereas the increase in heart rate, although of longer duration, rarely persists more than a few minutes. In the average normal person, the effect of cyanide has disappeared in 3 to 5 minutes, so that the administration may then be repeated.

The change in respiration caused by cyanide is eminently suited for the rôle of signal reaction. The abrupt onset and conspicuous increase in amplitude occur at any phase of the normal respiratory cycle and can be promptly detected and accurately registered either by graphic registration or by stopwatch.

The time elapsing between the arrival of cyanide and ensuing increase in respiration is a negligibly small fraction of the entire reaction time of cyanide. The unusual sensitivity of the respiratory mechanism to cyanide, the abrupt nature of the reaction and, most important, the close agreement between circulation time and reaction time leave little room for doubt that reaction occurs immediately after arrival of cyanide in the carotid sinus.

The simplicity of the cyanide method, which requires only a syringe, cyanide solution and stopwatch, makes possible its prompt application by one person in practically any position or condition in which the subject may be. Additional observations during exercise in this laboratory,²² and in pathological conditions,²³ confirm the feasibility of its use under a variety of conditions.

The reliability of the reaction time as an accurate measure of the circulation time in large vessels has been demonstrated by the agreement between the results obtained with the cyanide method and with the radium emanation and glucose methods known to exclude the circulation time in small vessels. Additional evidence concerning the cyanide pathway has been provided by the consistent disagreement with the histamine method known, on the other hand, to include the circulation time in small blood vessels. According to this evidence the cyanide method measures the circulation time to a large artery, which would imply that the respiratory stimulation is initiated in or near a large vessel. The close correspondence between the reaction time of cyanide and the circulation time of the blood to the carotid artery lends support to this thesis, and is consistent with the location of the site of cyanide action in the carotid sinus in man.

Separate estimations of the venous and pulmonary circulation times have been feasible with the cyanide method, and the accuracy of these measurements verified by comparison with the radium emanation method.

The cyanide method measures the pulmonary circulation time between the jugular vein and the carotid artery in man, which is the identical pathway measured in animals by Stewart²⁴ with the aid of his conductivity method. The application of the cyanide method for measuring the venous circulation time in various regions of the body and in the various portions of the same vessel has been described, and the feasibility demonstrated by studies in normal subjects.

SUMMARY AND CONCLUSIONS

1. Sodium cyanide in amounts sufficient to stimulate respiration has been injected intravenously in thirty-five normal individuals, and the effects on the circulation and respiration have been observed.

2. The optimal dose of cyanide varied with the weight of the subject and with the site of injection. The average optimal dose for injection into the antecubital vein was 7 mg., corresponding to 0.35 c.c. of 2 per cent solution of sodium cyanide or 0.11 mg. per kg. With jugular vein injections a comparable effect was obtained with approximately two-thirds of the antecubital dose. For foot injection, one and one-half times the antecubital dose were required.

3. The time elapsing between injection and the occurrence of increased respiration corresponded closely to the circulation time.

4. A simple method that registers the circulation time graphically and automatically is described.

5. Two sites of injection were used for measurement of pulmonary and peripheral venous circulation times: (1) The external jugular vein of the neck which measures the pulmonary circulation time; (2) the antecubital vein of the forearm or a superficial vein of the foot which measures the arm-to-carotid or foot-to-carotid circulation time. By difference the arm or leg venous circulation time is derived.

6. The average arm-to-carotid circulation time in thirty-five normal subjects was 15.6 seconds; it varied between 9 and 21 seconds. The average jugular-to-carotid or "crude pulmonary circulation time" in twenty-one subjects was 10.6 seconds, ranging from 7 to 14 seconds. The average arm index of venous velocity was 4.5 seconds. In 10 individuals the venous circulation time from the foot was found to be 15.1 seconds.

7. The reliability of the reaction time of cyanide as a measure of the velocity of the blood flow has been shown by the remarkably close agreement with the circulation times obtained with the radium emanation and glucose methods.

8. The reaction time of cyanide was constant when sudden clear-cut respiratory reactions were obtained, even though their intensity varied considerably.

9. Repeated estimations of the circulation time with cyanide were feasible after such short intervals as 3 to 5 minutes. Repeated estimations varied 2 seconds or less.

10. Evidence is presented that cyanide exerts its action upon the carotid sinus in man.

11. The cyanide method is a simple, reliable and objective method for estimating the velocity of blood flow of the various circulatory pathways of man.

We wish to express our appreciation to Dr. Benedict F. Massell for his assistance in this study.

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A METHOD FOR OBTAINING BLOOD PRESSURE BY ARTERIAL COMPRESSION AND SIMULTANEOUS CAPILLARY OBSERVATION*

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THE ordinary methods for obtaining blood pressure readings in man are dependent upon detection of a pulsation either by palpation, auscultation, or by recording instruments. In the occasional case in which there is no pulsation the only method available is direct cannulization or needling. Although needling, that is, arterial puncture, can be done with impunity by the experienced, in the hands of the inexperienced it may involve considerable pain and even a slight risk of local damage. It should also be noted that the operator usually locates the brachial artery by palpation before inserting the needle. When there is no pulsation, this guide is lost and the difficulty of the procedure is increased.

In 1930 a patient of Dr. Francis Grant was admitted to the University Hospital on the neurosurgical service of Dr. C. H. Frazier, and subsequently transferred to the ward of the medical clinic. This man presented a number of interesting clinical features which will be reported separately by Drs. M. Bowie and L. H. Collins. For the purpose of this communication it is sufficient to state that he was a man aged forty-two years with aneurysm of the aorta presumably luetic, a blood pressure in the legs varying between 216-162 systolic and 100-44 diastolic, and a complete absence of pulsation in the neck or upper extremities. In addition, he was subject to curious cerebral attacks, at times consisting of blindness, at times of syncope, and at times of actual convulsions. Considerable interest centered around the question of the blood pressure in the arms, which could not be obtained by the usual methods. One of us (J. Q. G.) was at that time making certain clinical capillary studies in connection with another problem, and it was suggested he study this patient. Accordingly a series of observations were begun which were interrupted by the patient's departure from the hospital. The principle employed in these first observations was that the brachial artery was occluded by the blood pressure cuff when capillary flow could not be seen, and was not occluded when flow could be seen. This was in agreement with the work of E. Weiss.¹ It was not realized at that time, however, how long the flow in the minute vessels could continue after brachial occlusion. Subsequently the method was perfected, using normal subjects, so that when the patient returned to the hospital in 1932 it was possible to repeat the observation, this time

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with consistent and satisfactory results. After readings had been obtained by this indirect method, one of us (L. H. C., Jr.) secured a direct reading by puncture of the brachial artery.

Method: A microscope lamp with a 500-watt bulb is set up so that its rays fall on the stage of a microscope at an angle of 45° . A spherical liter flask filled with distilled water is interposed between the lamp and the stage, serving to absorb heat and also acting as a lens to concentrate the light at the center of the stage. An ordinary microscope is used with a 5 ocular and a 32 objective. On the side of the microscope opposite to the lamp pillows are placed to support the patient's arm. One of the patient's fingers, usually the fourth, is inserted into a small wooden box. This box is shaped like a trough, with high sides but cut down ends. The finger is gently supported on the sides by plasticine and the box placed directly on the stage, with the arm resting on the pillows. A drop of immersion oil is then placed on the selected finger just back of the nail, and observation is begun.

The area chosen is that just back of the limbus where invariably one sees at least one row of hairpin shaped capillaries coursing parallel to the skin. If this area has been destroyed and observations must be made on more proximal capillaries where only the tips are visible, the procedure is much more difficult. A detailed description of the usual capillary bed has been taken up in a previous article.*

It is most important to select capillaries favorable for observation. At this magnification individual red blood cells cannot be seen, and most of the capillaries show as solid red bands. The phenomenon to look for is that commonly known as "granular streaming," which is shown when groups of red cells, usually five to ten in number, sweep along in clumps. When this is not present, blood flow is practically indetectable. Granular streaming is normally present in a few capillaries, but it can be readily produced in many capillaries by placing a blood pressure cuff about the arm and pumping it up to thirty or forty millimeters of mercury pressure. Capillaries which show granular streaming under these conditions will also show it under the conditions of the actual determination, and may therefore be regarded as suitable. It should be stated that the large red capillaries are usually the poorest for observation, for in them the cells are clumped and the flow is sluggish. Also, the best place to observe motion is at the junction of the arterial with the intermediate portion of the loop, that is, just at the arterial side of the tip. After a suitable capillary or capillaries have been selected, the finger box is moved so that the desired area is in the center of the field. If the armlet cuff has been partially inflated, it should be completely deflated and a rest of at least two minutes allowed.

It is now time to take the actual reading. The blood pressure cuff is quickly pumped up to a point above systolic pressure and clamped while the capillaries are watched. Ordinarily flow will continue for about a minute, perhaps a little more or a little less; and then certain of the capillaries, especially those which previously showed granular streaming, will appear to be filled with stagnant granules. If the flow does not stop, it means that a point above systolic pressure has not been reached. There may be slight to and fro movements of the granules, but there should be no definite stream. Many of the capillaries, of course, continue to maintain the appearance of solid red bands.

The pressure in the cuff is now slowly lowered, and the point where flow first definitely returns is read on the manometer. This is taken as systolic pressure. For the first reading it is well to lower the pressure slowly but steadily so as not to take too much time and cause the patient too much discomfort. Thus an approximate reading is obtained, which is too low. Then, after a few minutes' rest the procedure can be repeated, this time raising the pressure to twenty millimeters above the approximate

reading, waiting for cessation of flow, and then dropping it very slowly, so as to obtain as accurate a reading as possible. When properly done, the end point is very clear and definite.

SOURCES OF ERROR

If the nail beds have been traumatized, as by manicuring, the procedure is difficult because the most favorable areas for observation have been destroyed. In negroes the method is impossible because of the pigment. Observation is difficult in those with marked tremor. This may be corrected to some extent by strapping the box to the stage with adhesive tape.

It is theoretically possible that some cases may be found in which the capillary flow cannot be entirely stopped regardless of the pressure in the armlet applied in the usual way. Lewis² has shown that blood flow in the forearm is not entirely stopped by the ordinary cuff because of some anastomoses which pass through the bone itself. In some of his work he was forced to use a cuff extending from shoulder to elbow. This difficulty has not been met by us clinically. However, since realizing this possibility we have learned that the effect of Lewis' broad armlet can be obtained with the ordinary cuff if it is placed so that its lower portion includes the upper portion of the elbow joint. We have taken this precaution in our later cases, though for all practical purposes it seems not to have made the slightest difference.

It is possible that localized arteriolar constrictions might lead to localized capillary flow in the absence of flow in the larger vessels. To the best of our knowledge we have not seen this clinically, though to and fro movements are common. We believe that this factor can be eliminated if repeated observations made on different capillaries be found to be in close agreement.

One would expect that all readings would be a little low if the mercury were permitted to drop steadily, for there must be an appreciable period between the release of pressure in the brachial artery and initiation of flow in the capillaries. Our results would seem to support this, but the more slowly the pressure falls, the less the error.

Finally, it has been suggested that in cases of increased venous pressure the flow may not begin until the pressure is definitely below systolic.¹ We have no data concerning this, but have taken the precaution of raising the pressure quickly above systolic at the beginning; and, if there has been a preceding period of venous congestion, we have always allowed several minutes' rest before starting a determination.

It must be remembered that all factors causing fluctuations in blood pressure will be as operative in this method as in any other. Thus we found it absolutely necessary to allow a patient who has just come upstairs from a ward at least five or ten minutes' rest, with a blood pressure cuff in place, before starting actual determinations. In practice, this period can readily be utilized in the selection of suitable capillaries.

RESULTS

A considerable number of persons were observed in whom the blood pressure could be obtained in the usual manner, that is, by auscultation. The systolic blood pressure obtained by capillary observation was found to vary between five and twelve millimeters of mercury lower than that obtained immediately afterward by auscultation. As examples the first five cases studied are listed, though the others varied within the same range.

CASE	SYS. B.P. (AUSCULTATION)	SYS. B.P. (CAPILLARY METHOD)
1	138	130
2	108	98
3	112	105
4	112	110
5	168	162

The patient with absence of pulsation in both arms was then reexamined. In his case it would seem to be correct to speak of mean pressure rather than systolic pressure in the brachials. It is to be recalled that blood pressure in the legs was 182/80 at the time of the determination. Readings by capillary method were unusually clear and easy to obtain. Mean pressure was found to be 38 mm. of mercury in the right arm and 35 mm. in the left.

This unusually low reading was not anticipated, though it was recognized that if such figures could be taken as applying to the cerebral circulation they might readily account for the peculiar attacks of syncope and convulsions. Therefore, one of us (L. H. C., Jr.) attempted to measure the intra-arterial pressure in the upper extremity by a direct procedure. Though the brachial artery could not be palpated, the skin and subcutaneous tissue overlying the normal anatomical site of the artery were infiltrated with 1 per cent novocaine. A No. 12 gauge steel needle connected to a 10 c.c. Luer syringe with a threeway stopcock intervening between the two was used. The side arm of the threeway stopcock was connected by a piece of short rubber tubing to glass manometer tubing 1.5 mm. in diameter.

The left brachial artery was found to be in normal position and was entered without difficulty. After about 3 c.c. of blood had entered the syringe, the stopcock was turned and the blood allowed to flow into the vertical manometer tubing. On repeated observations the maximum height to which the blood column rose was 410 mm. No pulsation was observed in the level of the blood in the manometer. If correction is made for the specific gravity of blood and of mercury, this gives a direct intra-arterial pressure of 32.2 mm. of mercury. This compares fairly well with the reading of 35 mm. obtained by the indirect capillary method.

SUMMARY

A method is described for obtaining blood pressure in the brachial artery by brachial compression with a blood pressure cuff and simultaneous ob-

ervation of blood flow in the digital capillaries of the nail bed. This method consists in occluding the brachial artery with a pressure above systolic, waiting for cessation of flow in the digital capillaries, then slowly lowering pressure until flow is just resumed. This point is taken as systolic pressure or, in a case without pulsation, as mean pressure. As the method does not require pulsation, it is especially valuable in those cases in which pulsation is absent. Results obtained are compared with those obtained by auscultation in normal persons. One patient without pulsation in the brachial arteries was studied, and the results were confirmed by a direct pressure reading after arterial puncture.

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STUDIES OF THE ELECTRICAL FIELD OF THE HEART.

I. INVARIANTS OF THE ELECTROCARDIOGRAM*†

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IT WAS the variability in the appearance of the electrocardiographic deflections that led Einthoven to advocate the use of the standard three leads. He believed that these leads would give a better idea of the potential set up by the heart than would one lead alone. This variability in appearance has also been shown to exist among leads other than the standard three usually employed (Cohn,¹ Wilson²). In addition, it has been shown that the appearance, especially the amplitude, of the deflections is dependent upon the electrical resistance of the tissues between the heart and the electrodes and on the electrical shunting of the body fluids. Both of these are quantities which vary with the leads employed as well as with other conditions (Zeisler,³ Katz⁴). Every electrocardiogram is dependent on (1) the electrical changes in the heart muscle, (2) extracardiac factors independent of the particular lead employed (e. g., pericardial effusion, emphysema, etc.), and (3) extracardiac factors depending on the particular lead employed.

It was the purpose of this research to see whether or not the durations of the various intervals and deflections, the algebraic sum of the deflections in the QRST interval, and Einthoven's quantity were independent of the lead employed. Any quality of the electrocardiogram which is independent of the lead employed we have designated as an *invariant*.⁵ Einthoven's quantity is defined as follows: If from two electrodes A and B the wires are so connected to the galvanometer that a current passing through the galvanometer from B to A gives an upward deflection, then the lead is called AB, or the lead from A to B; if the wires are reversed, the lead is BA. Let any three points A, B, C be connected so as to give the leads AB, BC, AC, called I, II, III respectively. Let the deflections at simultaneous points of the electrocardiograms of these leads be e_1 , e_2 , e_3 respectively. The quantity we wish to consider is $\Delta = e_2 - e_1 - e_3$. For the three standard leads Einthoven's law is $\Delta = 0$. It has been stated that Einthoven's law $\Delta = 0$ is exactly satisfied for *every* three leads AB, BC, CA (Wilson et al.⁶). Furthermore, Wilson et al.⁷ have attached significance to the algebraic sum of the deflections in the QRST interval.

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PROCEDURE

Electrocardiograms with a large number of leads (about 150) were taken on a single individual. The electrodes consisted of circular sheets of German silver about 4 cm. in diameter, each with a binding post, shielded from moisture, to accommodate two wires. The electrodes were placed on various parts of the skin with a paste of flour and concentrated saline. Electrocardiograms were recorded on one film from two leads simultaneously. The location of simultaneous points on the two leads was determined by measuring the phase difference between the two curves of the same lead recorded simultaneously by both instruments. This was, of course, essential in calculating the Einthoven expression.

RESULTS

In every lead in our subject (as shown in Figs. 1, 2 and 3) the record consisted of a sequence of cycles of deflections (or waves) corresponding to the cycle of the heart beat. The sequence, though not regular, was the same in all leads. Each cycle was composed of two sets of deflections, the auricular and ventricular, the latter made up of an initial and final complex, often separated by an approximately isoelectric line. This division into P, QRS and T is independent of the particular lead used; the fact that in some leads the P or the T complex is not seen does not alter this division, for such a curve may be considered a special case in which the P or the T complex is isoelectric. Hence the sequence of cycles of deflections, the rhythm of the sequence and the division of each cycle into three groups of deflections, the P, QRS and T, are invariants.

The intervals of the cycle were not all easily measured because the beginning of T and sometimes the beginning of P were not sharply demarcated. It was found most convenient to measure (1) the duration of P, (2) the time interval between the beginning of P and the beginning of QRS, the so-called P-R interval, more properly called the P-Q interval, (3) the duration of QRS, (4) the time interval between the beginning of QRS and the beginning of T, the Q-T interval,* (5) the time interval between the beginning of QRS and the end of T, the QRST interval.

In the various different leads taken by us on any one day the maximum and the minimum P-Q intervals never differed by more than 0.03 sec., and in two simultaneous leads never by more than 0.02 sec. With many additional leads it was found that this range is not increased, so that P-Q is an invariant within 0.03 sec.

In some leads the P complex is so small that it is seen with difficulty, but where it can be seen its duration does not vary from lead to lead by more than about 0.01 sec. The beginning of QRS is always seen and the end of QRS usually; the duration of QRS does not vary by more than about 0.01 sec.

*Q-T has been given other meanings but in this report will be used in only the sense here defined.

It may be impossible to measure accurately the S-T interval because the beginning of T cannot always be seen. This is due to the fact that S-T is

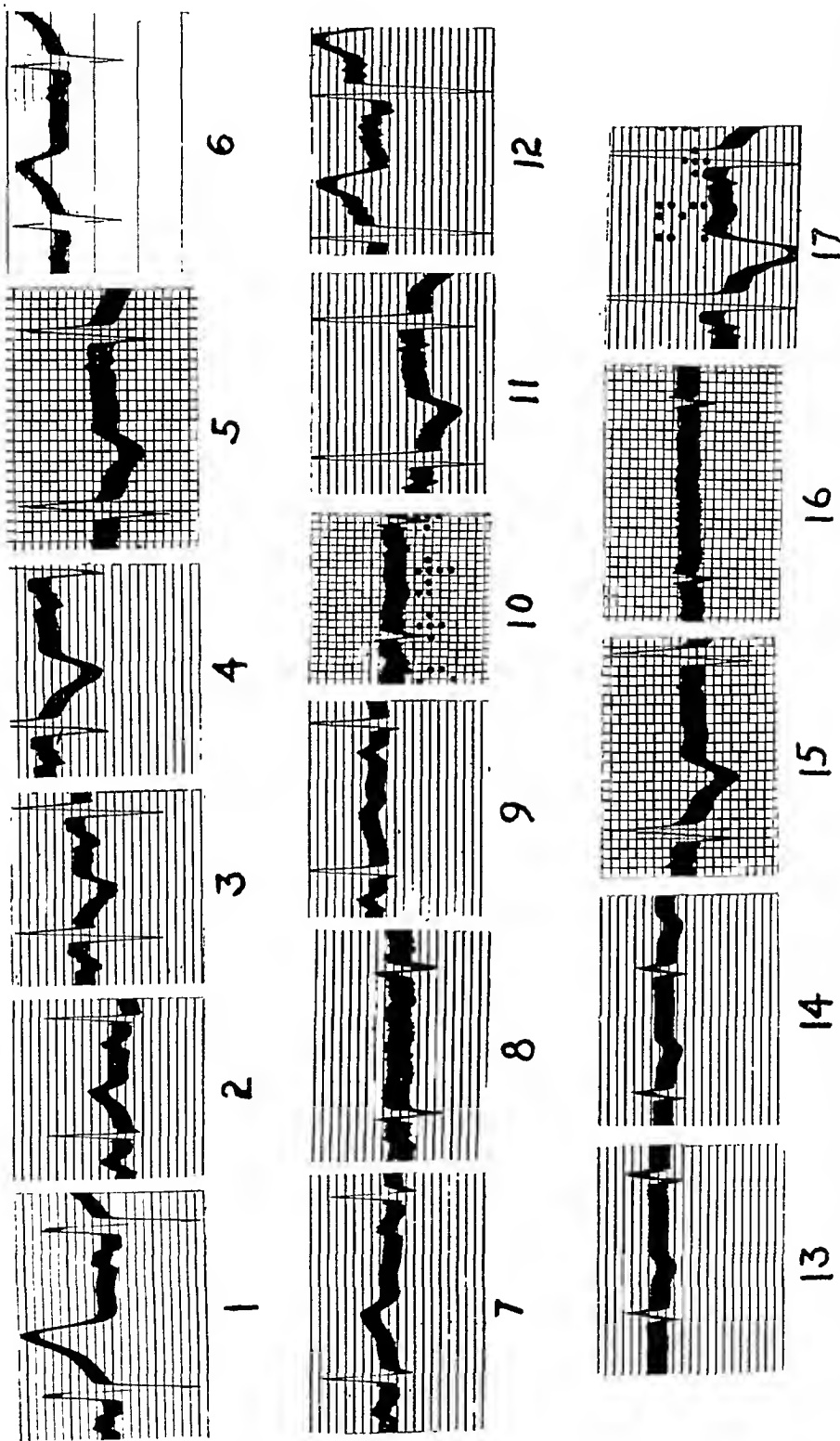


Fig. 1.—The curves, from the same person with different leads, are selected to show the following: leads 1 to 7, variability in P; leads 2, 8, 9, 10, 11, 12 the variability in QRS; lead 11, deep Q; leads 13, 14, 15 notching and splintering of QRS; leads 1, 4, 7, 9, 13, 16, 17 variability in T; leads 1, 11, 12 variability in S-T.

very often not isoelectric and often not horizontal. In Fig. 1, Lead 1, for example, it is not possible to see just where on the rising limb of the S-T

segment T begins. When the beginning of T is clearly seen, it is found that the Q-T interval is very nearly invariant, just as is the P-Q interval; if this interval is measured from the beginning of QRS in those leads in which the beginning of T is not seen, a point is found on the curve which appears as though it may very well be the beginning of T. Hence for

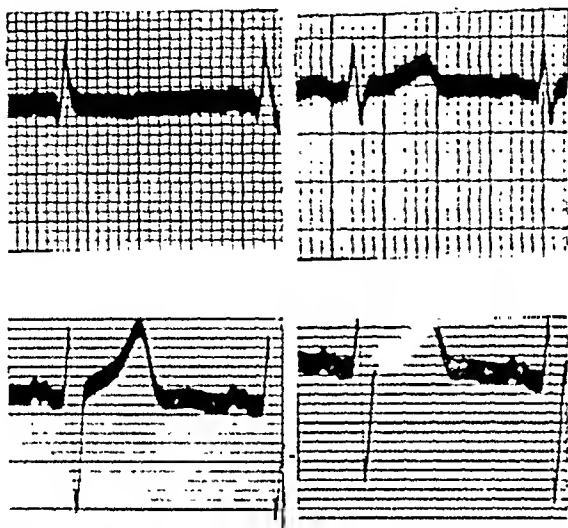


Fig. 2.—The leads of the figure form an Einthoven triangle. The Einthoven expression was calculated for this triangle by using simultaneous points of the curves of the two leads. (Note the difference in appearance of the common lead in the two segments of the figure—top lead in each. The explanation for this will be discussed in a subsequent paper.)

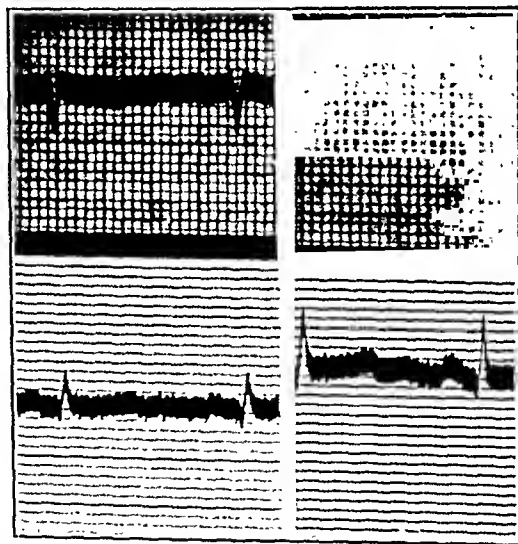


Fig. 3.—The leads of this figure form another Einthoven triangle. The Einthoven expression was calculated for this triangle also. (Note, for contrast, with Fig. 2, the similarity in appearance of the common lead in the two segments of the figure—top lead in each.)

practical purposes Q-T is an invariant and therefore S-T is also an invariant. Similarly, it is found that QRST is an invariant within about 0.02 sec.

Consequently, all the time relations of the electrocardiogram are invariants, namely, the duration of P, of QRS, of QRST, the P-Q interval, the S-T interval, and therefore also the duration of T.

In Fig. 1 are shown selected leads illustrating the wide variation in direction, number of phases, amplitude, contour, slope, slurring, notching and splintering of the P-wave (leads 1 to 7), QRS complex (leads 2 and 8 to 12) and T-waves (leads 1, 4, 7, 9, 13, 16 and 17). Attention is drawn to the deep Q-wave in lead 2 in this normal individual, which indicates that this wave, to which some significance has been attached, is not an invariant. In leads 13, 14 and 15 there is notching and splintering of QRS, not near the base line, and in lead 15 this occurs in a relatively large deflection. This has been considered significant by Pardee,⁸ but as this study shows, slurring and notching of QRS are not invariants. It is apparent that the slope of a deflection is completely determined by its amplitude and its duration, and slurring is determined by the slope alone; for example, in lead 8 the deflections of QRS are slurred because their slope is smaller than in lead 12 where they are not slurred.

The segments between waves also vary in these leads. In lead 3 the curve between P and Q is above the isoelectric line, in lead 1 below. In leads 1, 11 and 12 are seen elevation and depression of S-T and variation in its slope.

An inspection of Fig. 1 will show that the algebraic sum of the areas between the deflections of the QRST interval and the base line of one cycle is obviously not an invariant⁷; in lead 2 it is small and positive, in lead 17, large and negative.

A similar analysis of the Einthoven quantity, which Wilson⁶ recently asserted, on theoretical grounds, to be equal to zero for any three points of the body, showed that it is not an invariant. For example, in Fig. 2 we found a pair of simultaneous points where $\Delta = -15.3$, in Fig. 3 a pair where $-2 < \Delta < 0$. In many other sets of leads Δ was found to vary between 0 and -15 . Consequently, it is *not* an invariant. (The explanation of this result in the face of theoretical arguments to the contrary,⁶ will be considered in a subsequent paper.)

DISCUSSION

This analysis of multiple leads shows that the only known invariants of the electrocardiogram are the time relations of the various deflections and the intervals between them. It is to be distinctly understood that we do not imply that the invariants are important and the noninvariants unimportant. In this paper we are simply differentiating those qualities of the electrocardiograms which are independent of the lead employed from those which vary with the lead. Too often significance is attached to changes in configuration in standard leads which might be due to alteration in the heart's position (cf. Katz and Ackerman⁹). The theoretical explanation of the observed results, and the significance of the invariants and of the noninvariants will be discussed in a subsequent paper.

SUMMARY

1. Every electrocardiogram depends on the electrical changes in the heart muscle and on extracardiac factors, some of which are independent of, and others dependent on, the particular lead employed.

2. By using many different leads (about 150) on one individual the invariance of various properties of the electrocardiogram was investigated to determine which properties were invariants, i. e., independent of the particular lead used.

3. The only known independent invariants of the electrocardiogram are its time relations, namely, the sequence of cycles, their rhythm, the division of each cycle into three complexes, the duration of P, of QRS, of QRST, of T, and of the P-R (P-Q) and S-T intervals.

4. All other properties studied, such as direction, amplitude, contour, notching, slurring, the algebraic sum of the initial and final ventricular deflections, and the Einthoven quantity were found to be noninvariants.

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ELECTROCARDIOGRAPHIC FINDINGS IN TUMORS OF THE HEART

WITH A REPORT OF A CASE*

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THE literature contains many reports of cases of cardiac tumors. Most of these reports are concerned with clinical and pathological findings and with discussions of the frequency and location as well as the character of the cardiac neoplasms. There is also a considerable number of reports of cardiac tumors in which electrocardiograms were obtained, but in only three of these are records presented.

These electrocardiograms do not show any uniformity of findings but, as might be anticipated, vary according to the chamber of the heart in which the tumors were located.

These deviations from normal are shown graphically in Table I.

The records obtained in the present case show remarkable resemblances to those obtained in cases of recent coronary thrombosis, but also have definite characteristic features which serve to distinguish them from those reported in such cases. Contrary to expectation there were no disturbances of the coronary arteries either by tumor cells or by arteriosclerosis or thrombi.

The purpose of this paper is to present the clinical and pathological findings in a case of metastatic tumors of the myocardium and to present the fourth series of electrocardiograms reported in patients with cardiac tumors.

Both primary and secondary tumors of the heart have been reported by many authors and for the most part were diagnosed only at post-mortem examination. In a series of 37,777 autopsies reported by Morris,⁴ Willis and Amberg,⁸ and Peters and Milne,¹⁴ 159 cases or approximately 0.4 per cent showed secondary tumors of the heart. At this hospital three cases of metastatic tumors of the heart have been found in 592 autopsies, which is approximately 0.5 per cent. These three cases, including the one in this report, are all those of lymphosarcoma, the first two showing nodules in the wall of the left auricle without clinical evidence of cardiac involvement. Of these 592 autopsies 44 (approximately 7.4 per cent) were in cases of malignant disease.

Metastases to the heart have occurred from all the principal organs of the body in which malignant tumors are commonly found, and have reached the heart by three routes: (a) by lymphatic vessels, (b) by

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invasions of veins and tumor cell embolisms through blood vessels, (c) by direct extension from a tumor in the vicinity of the heart. (Kauffman.¹²) Morris believes that tumors are carried to the heart by the blood stream in most instances. In the case here reported metastases occurred apparently by lymphatic or blood vascular route, although no tumor thrombi could be demonstrated in the vessels.

Most observers (Kauffman,¹² Napp¹³) state that the right side of the heart is more often involved than the left. In our case the muscular wall of the left ventricle and interventricular septum are extensively involved.

TABLE I

AUTHOR	LOCATION OF TUMOR	RHYTHM	AXIS	P-R INTERVAL	QRS INTERVAL	QRS COMPLEX	T-WAVE	S-T SEGMENT
Lloyd ⁷	A-V Node	Normal sinus	Normal	.17-.28 sec. Dropped beats	Normal	Normal	Upright	Isoelectric
Willius & Amberg ⁸		Normal sinus	Right deviation	.12 sec.	Prolonged .12 sec.	Notched	Inverted in II & III. Upright in I	Elevated in I and II, depressed in III, convex
Houck & Bennett ⁹	Left auricle	Normal sinus tachycardia	Normal	.16 sec.	Normal .08 sec.	Low voltage	Slightly diphasic I & II (digitalis?)	Concave (digitalis?)
Siegel & Young	Left ventricle and septum	Sinus tachycardia	Normal	.16 sec.	Normal .04-.06 sec.	Normal	Inverted all leads	Convex slightly depressed II and III

Statements as to the relative frequency of sarcoma and carcinoma found in the heart are conflicting. Authors (Morris, Willius and Amberg) who believe that secondary carcinomas are more frequent may not really be in serious disagreement with others (Kauffman) who believe that sarcomas are more frequent since, as Goldstein² states, "There are probably many cases of secondary sarcoma of the heart that are never reported in the literature. They are comparatively not much less common than secondary cancer of the heart."

The clinical picture of tumor of the heart is variable, and there are no pathognomonic signs (Morris). At the time he wrote (1927) the condition had never been diagnosed *intra vitam*. The case of reticulum cell sarcoma with metastases involving the wall of the ventricle here reported is of interest in that the tumor of the heart was suspected *ante-mortem* because of certain electrocardiographic findings.

Armstrong and Mönckeberg¹ in 1911 reported a case with a Jacquet polygraphic tracing which showed complete auriculoventricular heart-block. This tumor was primary in the heart.

Darier³ in 1927 published a report of a cardiac tumor which he found in a case of mycosis fungoides. Tumors causing a clinical syndrome resembling subacute bacterial endocarditis have been reported by Carnot and Lambing in 1928.⁵

Lloyd⁷ published in 1929 the first electrocardiogram in a proved case of tumor of the heart. His tracings showed sino-auricular rhythm with a P-R interval up to 0.28 seconds, thus constituting first degree A-V block. The tumor was found in the region of the A-V node and was probably an endothelioma.

Willius and Amberg⁸ in 1930 reported two cases of metastatic tumor of the heart, one of which was diagnosed ante mortem. Their electrocardiograms of one case, a child of eight years, showed incomplete bundle-branch block, with negative T-waves in Leads II and III and a slight elevation of the S-T segments in Leads I and II with a depression of the S-T in Lead III. There was also a moderate degree of right axis deviation. Clinically the patient showed signs of myocardial failure. Postmortem examination showed a metastasis from an endothelioma of the left femur. A second electrocardiogram taken one month after the first was essentially unchanged. Their second case was one of leucosarcoma of the heart in a child of two and a half years. No electrocardiograms of this case were published.

Houck and Bennett⁹ in 1930 reported a tumor of the left auricle (polypoid fibroma) in which the electrocardiogram showed sinus tachycardia with a rate of 120. The ventricular complexes were somewhat abnormal and the electromotive force was low. The T-waves in Leads I and II were slightly diphasic. However, their patient had received digitalis before admission to the hospital, so that these T-wave abnormalities may have been due to the drug.

Fishberg¹⁰ in 1930 reported three interesting cases in which secondary malignant growths in the right auricle were accompanied by auricular fibrillation or flutter which led during life to the opinion that the known malignant tumor had invaded the right auricle. He did not publish any electrocardiograms.

Yater¹¹ in 1931 gave a comprehensive review of all the literature and reported nine cases of his own. He published no electrocardiograms.

CASE REPORT

Clinical Summary.—N. M., aged forty-seven years, Italian, gardener, was first seen January, 1931, presenting himself with a complaint of a "lump" in the left lower abdomen of two months' duration. This mass was painful and was increasing in size. There were no other significant symptoms. However, he had lost fourteen pounds in weight since the onset of the illness. On January 23, 1931, he was seen

in consultation with the surgical service because of feeble heart sounds. At this time he denied precordial or substernal pain either at rest or even with severe effort. He was also positive that he had never noticed any dyspnea either nocturnal or diurnal, either at rest or with effort. He had never had any symptoms suggesting collapse or any severe epigastric pain.

On examination the patient was found to be poorly nourished and somewhat pale. He was not dyspneic and there was no orthopnea or distention of the veins

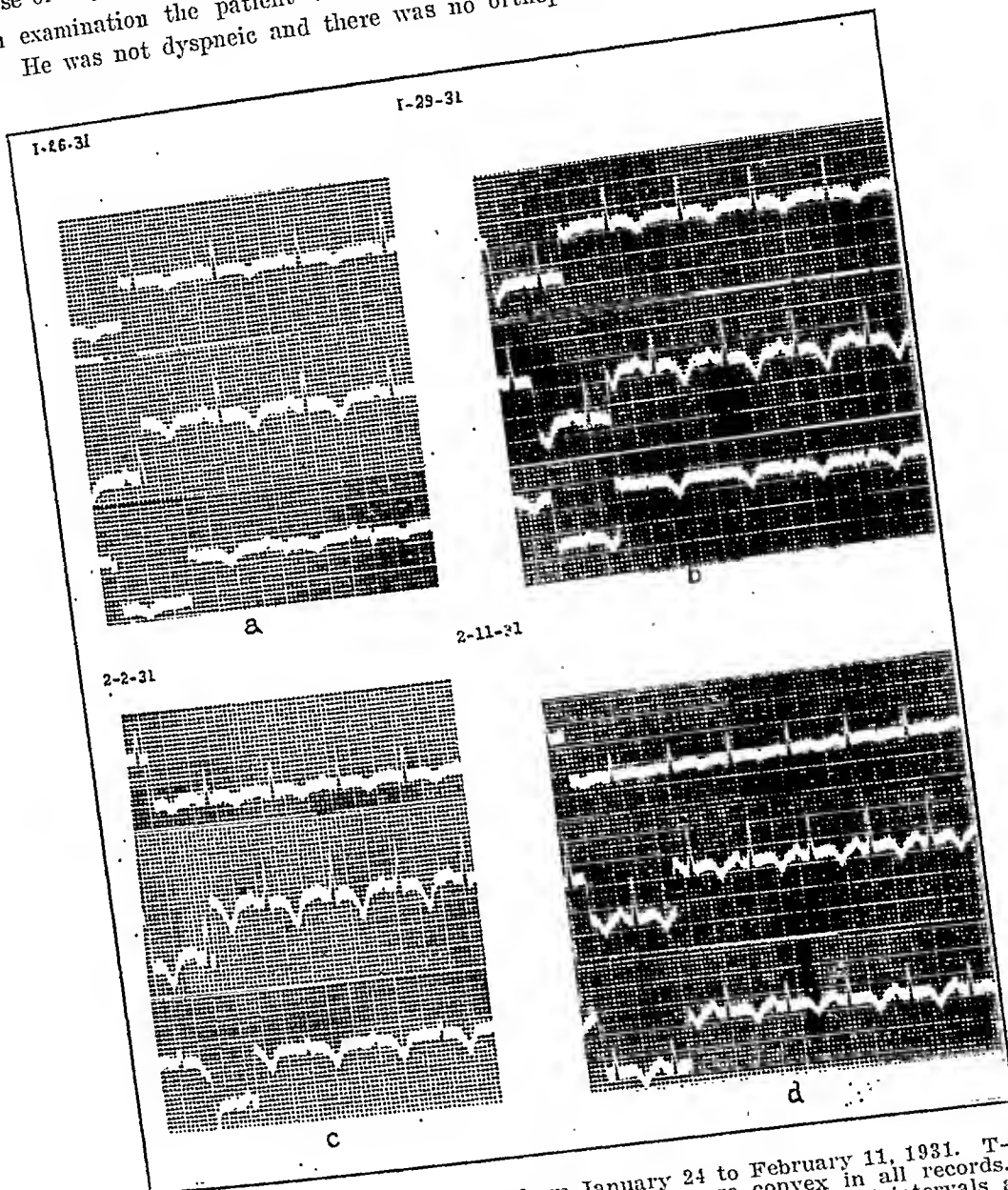


Fig. 1.—Electrocardiograms taken from January 24 to February 11, 1931. T-waves inverted in all leads in all records. R-T segments are convex in all records. The T-waves are "cove plane" in all leads. Duration of P-R and QRS intervals are all within normal limits. "Take-off" of T-waves is isoelectric in all records. Note the lack of significant change during this time.

of the neck. The lungs were free from abnormal signs, but the heart sounds were weak and distant. It was this finding which first drew attention to the heart and which prompted the request for the medical consultation and the electrocardiogram. The heart was not demonstrably enlarged and no murmurs were heard. The rate was 86 per minute and the pulse was rhythmic and regular. There was moderate peripheral arteriosclerosis with a blood pressure of 92 mm. systolic and 68 mm. diastolic. The liver was palpable but the spleen and kidneys were not. In the left

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upper quadrant of the abdomen there was a hard nodular mass which seemed to be about ten centimeters in diameter. This was not movable. There was no enlargement of the palpable lymph nodes. Neurological examination was negative. The tentative diagnosis was malignant disease of the colon.

Laboratory Findings.—On admission the urine contained a faint trace of albumin, and tests for urobilin and urobilinogen were strongly positive. No blood was present in the urine either grossly or microscopically. Slide precipitation tests for syphilis and Wassermann reaction were negative. Red blood cells numbered 3.2 million per c. mm. Hemoglobin was estimated at 65 per cent (Tallqvist). White blood cells numbered 19,000 per c. mm. Differential count of leucocytes showed polymorphonuclear neutrophils 88 per cent; lymphocytes 11 per cent; others 1 per cent. There was slight anisocytosis.

Roentgenoscopic studies of the gastrointestinal tract revealed no abnormal findings. A roentgenogram of the heart several days after admission showed moderate bulkiness of the left ventricle and some infiltration in the base of the right lung.

Electrocardiographic tracings recorded on four occasions are shown in Fig. 1. Fig. 1a is the record taken January 26, 1931. It shows normal sinus rhythm, normal QRS complexes in all leads and inverted T-waves in all leads. The S-T portion is isoelectric in all leads. The T-waves in Leads II and III have somewhat rounded shoulders. The duration of the P-R and QRS intervals is well within normal limits. (0.16 seconds and 0.04 seconds respectively.) Fig. 1b is a record taken three days later and resembles the first one except for a somewhat deeper inversion of the T-waves in Leads II and III and a somewhat greater rounding of the shoulders of the T-waves in all leads. Fig. 1c is a record taken four days later. This record shows still deeper inversion of the T-waves in Leads II and III and a somewhat shallower T-wave in Lead I. The convexity of the S-T segment is greater than in the two preceding records, especially in Leads II and III. The "take-off" of the T-waves is very slightly (1 mm.) below the isoelectric level.

Fig. 1d is an electrocardiogram recorded nine days after the one in c and shows the T-waves to be somewhat less deeply inverted than those of b and c. The "take-off" of the T-waves in Leads I, II and III is now slightly above the isoelectric level. The rounding of the shoulders of the T-waves in Leads II and III is slightly greater than that in the previous records.

The patient's course in the hospital progressed unfavorably. He developed pneumonia at the right base with sharp rise in temperature which was probably the cause of the infiltration observed in the roentgenogram. Recovery from this infection occurred. On February 11, he bled severely from the rectum, going into shock. Apparently the tumor had eroded into the lumen of the bowel. His blood count during the hospital stay fell to 2.6 million red blood cells per c. mm. and later to 1.2 million. The patient died on February 12, following the hemorrhage. A few hours before death a pericardial friction rub was heard over the entire precordium.

Autopsy Findings of Interest.—The case was one of reticulum cell or large round cell lymphosarcoma apparently arising in a mesenteric lymph node, with extension into the wall of the duodenum, and metastasis throughout the viscera including the wall of the left ventricle which was extensively involved.

The heart weighed 315 grams. There was a large tumor mass approximately 5 cm. in diameter involving about one-half of the wall of the ventricle and about one-third of the interventricular septum. On the external surface of the heart the tumor formed a slightly bulging mass grayish white in color extending toward the apex, the distribution of the tumor resembling that of an infarct due to occlusion of the descending branch of the left coronary artery. No tumor cell thrombosis of the large or small branches of the coronary artery was demonstrable, either grossly or microscopically. Tumor cells had, however, invaded the walls of the thin-

walled veins and in places projected irregularly into the lumen. The coronary arteries were thin-walled and free from arteriosclerotic changes and thrombi. The epicardium as well as the myocardium was invaded by tumor on the posterior surface of the heart. There were small tags of fibrous tissue invaded by tumor cells which were the only anatomical alteration which might have caused the pericardial friction rub heard clinically. In addition to the large tumor mass mentioned above, there was a small tumor nodule approximately 6 mm. in diameter just beneath the

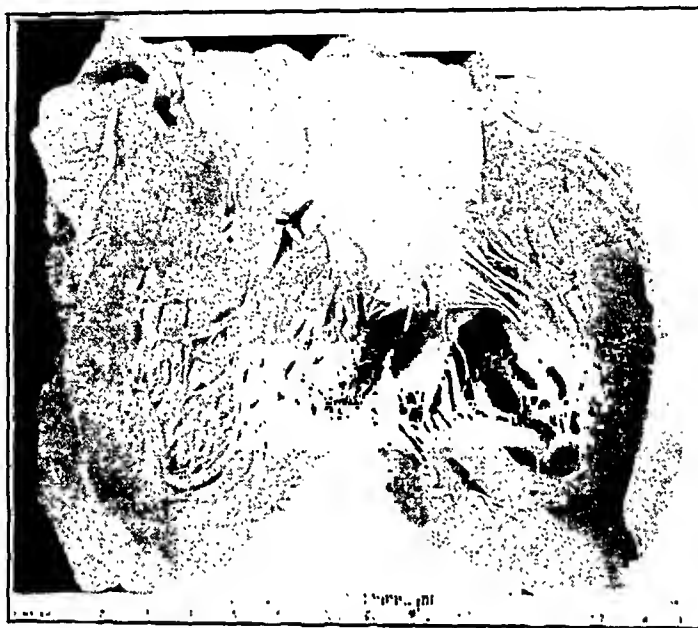


Fig. 2.

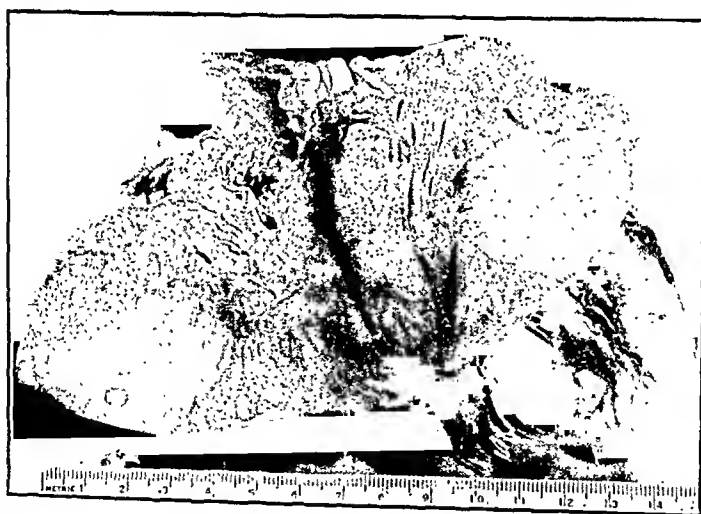


Fig. 3.

Figs. 2 and 3.—Metastatic reticulum cell sarcoma of the myocardium. Gross characteristics.

endocardium in the region of the undefended space. Sections through this nodule showed the tumor involving the myocardium only and not extending to the region of the conduction fibers or overlying endocardium.

The gross appearance of the tumor is seen in Figs. 2 and 3. Grossly, the tumor was of fine architecture and on careful inspection of the periphery of the tumor the myocardial fibers were still recognizable. This was borne out by its microscopic

appearance in which the cells were seen to infiltrate and separate the normal structures rather than destroy them, in this respect resembling the leucemic infiltrations rather than destructive tumors.



Fig. 4.—Photomicrograph, low-power magnification, metastatic reticulum cell sarcoma of the myocardium, extending through the epicardium.

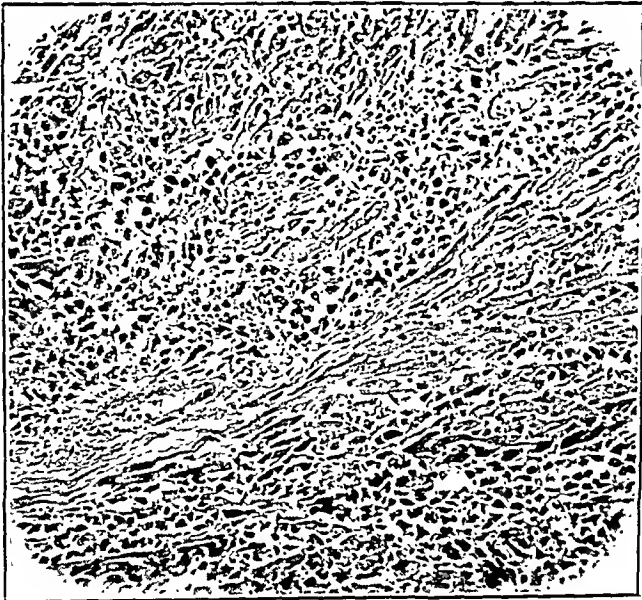


Fig. 5.—Photomicrograph, metastatic reticulum cell sarcoma of the myocardium, showing the tumor cells infiltrating the muscle fibers.

The largest tumor mass in the body was in the mesenteric fan extending into the wall of the duodenum with ulceration of the wall. The distribution suggested that the tumor arose in the mesenteric lymph nodes or possibly in the lymphoid tissue of the duodenum. In addition to the metastases in the heart there were secondary tumors in the kidneys, spleen, mesenteric lymph nodes, serosa of the sig-

moid colon, right adrenal, and gall bladder. There were no metastases present in the lungs or in the liver.

The microscopic characteristics of this tumor in the heart are shown in Fig. 4. Round cells, varying considerably in size, predominate. The nuclei of these were large, hyperchromatic, and in many cases in mitosis. Some of the cells were polygonal, many of the nuclei were indented and many were multinucleated. The cells resembled those of germ centers of lymph follicles. Oxidase stains on frozen sections of the tumor showed no oxidase granules present. The tumor stroma was scanty.

DISCUSSION

When the electrocardiograms in our case were first studied, it was thought that the changes were produced by myocardial damage from coronary artery disease. In repeated questioning of the patient all symptoms of cardiac embarrassment, such as precordial, substernal or epigastric pain or dyspnea, either at rest or with effort, were denied. There were no physical signs of cardiac failure. X-ray examination of the heart did not reveal any significant abnormalities. In addition to all these observations, closer study of the tracings revealed that the T-waves were constantly inverted in all leads in every record, and their direction was not reciprocal in Leads I and III as is usually the case in recent coronary thrombosis. Moreover, there was no significant change from day to day as one would expect in recent coronary occlusion. The S-T segments of all the tracings were isoelectric or practically so. Accordingly, it was suspected that a metastasis in the heart was quite possible. This concordance in the direction of the T-waves in all leads associated with "cove-plane" T-waves and convex S-T segments without significant deviation of these S-T segments from the isoelectric level may well be dependent upon the changes induced in the electrical effects of the myocardium by the presence of the tumor.

From the records one would assume that the main divisions of the conduction system were preserved intact and such proved to be the case. These changes in T-wave direction were not produced by abnormally high skin resistance, for in such cases QRS waves and T-waves are altered in the same direction. Katz⁶ states that inverted T-waves are to be regarded as the result of a disturbance in the pathway of retreat which simulates persistence of activity in the region of the apex of the left ventricle. In other words there may be a delayed offset of activity or a relative prolongation of activity or both. Attention is called to the fact that this tumor occupied that portion of the left ventricle ordinarily supplied by the descending ramus of the left coronary artery. It should be remembered that the coronary arteries and their branches in this area were not obstructed by tumor cells, thrombi, or arteriosclerotic plaques.

SUMMARY

1. The case reports of tumor of the heart have been reviewed. Where electrocardiograms have been recorded, they have been analyzed and

compared with those recorded in our own case. The frequency of cardiac tumors together with their location in the heart has been discussed.

2. A case of metastatic cardiac tumor with electrocardiograms is reported.

3. The similarity of the electrocardiographic findings in a case of tumor of the heart and in myocardial changes from other causes is pointed out, especially the similarity of records in cases of coronary disease.

4. The distinctions between records of coronary disease and those of tumor are noted, especially the lack of reciprocal direction of T-waves in Leads I and III and the failure to show deviation from the isoelectric level in the S-T segments.

5. The changes seen in electrocardiograms in tumor cases give some evidence as to the location of the neoplasm in the heart.

We wish to express our indebtedness to Dr. Harold Feil and Dr. B. S. Kline for their valuable assistance in the study of this case and in the preparation of this paper.

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THE ELECTROCARDIOGRAM IN DIABETIC COMA*

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CORONARY sclerosis is comparatively common among diabetics as a group.^{1, 2, 3} Coronary occlusion is a recognized complication of diabetes, particularly in cases where the blood sugar has been rapidly brought down from a high to a low level by insulin treatment.^{3, 4} The signs and symptoms of coronary occlusion may be masked by diabetic coma. Therefore, it appears to us of practical value in the recognition of coronary disease in diabetic coma, to find out what effect, if any, diabetic coma itself may impose on the electrocardiogram.

In diabetic coma there are a number of known deviations from normal conditions which must be considered separately in regard to their possible effects on the electrocardiogram. The most evident of these are acidosis, hyperglycemia, uremia and low blood pressure.

Acidosis and Hyperglycemia.—It has been shown in experimental animals that slight changes in the P_{H} of the blood toward the acid side will cause a slowing of the sinus rhythm, delayed auriculoventricular conduction, marked changes in the ventricular complexes, lengthening of the refractory period of both auricular and ventricular muscle, and a tendency to the appearance of ventricular premature beats.^{5, 6, 7} However, no published data have been found to indicate that the degree of acidosis reached in disease is sufficient to cause such disturbances. It is true that the frequency of heart disease in patients with diabetes has led to the belief among some clinicians that diabetes exerts a specific toxic effect upon the myocardium, and reference has been made to a "cardiac type" of diabetic coma.⁸ Indeed, "the toxic products of the acetone bodies" have been incriminated as the agent causing failure in these cases and digitalization has been recommended.⁹ However, these clinical impressions have not been supported by electrocardiographic or pathological evidence. In a careful study of 123 diabetic patients Hepburn and Graham found no relation between the electrocardiographic abnormalities and the existing level of blood sugar or degree of acidosis.¹⁰

Uremia.—It is generally recognized that uremia, like many other intoxications, may have a depressant effect on the T-waves. Some of the electrocardiograms of patients with uremia, published by Wood and White, show T-waves of the characteristic "coronary" type.¹¹ The high

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TABLE I
OBSERVATIONS ON PATIENTS DURING COMA

CASE NUMBER	SEX	AGE	CLINICAL CONDITION*	BLOOD SUGAR IN MG. PER 100 C.C.	BLOOD CO ₂ COMBINATION POWER IN VOL. UNES PER CENT	BLOOD NONPROTEIN NITROGEN IN MG. PER 100 C.C.	RECTAL TEMPERATURE IN DEGREES FAHRENHEIT	BLOOD PRESSURE		RHYTHM	RATE PER MIN.	P-R INTERVAL IN SECONDS	QRS INTERVAL IN SECONDS	T-WAVE IN LEAD I	T-WAVE IN LEAD II	T-WAVE IN LEAD III	ELECTRICAL AXIS	REMARKS ON ELECTROCARDIOGRAM
								SYSTOLIC	DIASTOLIC									
1	F	25	Mild coma	180	22	47	100.2	110	80	Sinus tachycardia	115	0.12-0.14	0.08	Up	Up	Up	Normal	High skin resistance
2	F	19	Coma	440	17	27	99.8	120	86	Sinus tachycardia	110	?	0.08	Up	Up	Up	Normal	P-waves not clear
3	M	13	Coma	380	20	38	95	100	70	Sinus tachycardia	145	0.16	0.08	Up	Up	Up	Normal	High skin resistance
4	F	37	Deep coma	420	10	67	97	100	60	Sinus tachycardia	115	0.16	0.08	Up	Diphasic	Diphasic	Normal	High skin resistance
5	M	49	Coma	480	15	77	98	140	?	Sinus tachycardia	140	0.16	0.08	Up	Up	Inverted	Left	High skin resistance
6	F	46	Very drowsy	620	3	71	101.6	98	80	Sinus tachycardia	140	0.12	0.08	Up	Up	Diphasic	Normal	One ventricular extrasystole. High skin resistance
7	F	23	Deep coma	500	8	48	101	100	70	Sinus tachycardia	140	0.12	0.10	Up	Up	Inverted	Normal	High skin resistance
8	M	13	Coma	880	17	Not recorded	99.8	60	?	Sinus tachycardia	160	0.12	0.06	Up	Up	Up	Normal	High skin resistance
9	F	27	Deep coma	370	3	23	96	138	82	Sinus tachycardia	130	0.18-0.20	0.06	Up	Low	Diphasic	Normal	Slightly low origin T ₁
10	M	35	Deep coma	360	4	39	95.6	130	80	Sinus tachycardia	109	0.14	?	?	?	?	Normal	Deformed by high resistance
11	F	18	Coma	420	11	34	98.6	106	60	Sinus tachycardia	111	0.14	0.08	Diphasic	Diphasic	Diphasic	Normal	High skin resistance
12	F	38	Coma	270	8	35	97.2	120	80	Sinus tachycardia	107	0.16	0.08	Flat	Low	Flat	Normal	High skin resistance
13	M	13	Very deep coma	680	4	54	96.2	90	?	Sinus tachycardia	160	0.12	0.06	Up	Up	Inverted	Normal	High skin resistance
14	M	18	Coma	320	12	28	99	124	82	Sinus tachycardia	111	0.16	0.10	Up	Up	Inverted	Normal	High skin resistance
15	M	14	Deep coma	480	7	40	99.4	Not obtainable		Sinus tachycardia	130	0.14	0.08	Up	Diphasic	Inverted	Normal	High skin resistance

*In all cases examination of the heart was recorded as negative except in Case 15 in which it was noted that the heart sounds were "distant."

TABLE II
OBSERVATIONS ON PATIENTS AFTER EMERGENCE FROM COMA

CASE NUMBER	INTERVAL BETWEEN FIRST AND SECOND OBSERVATIONS IN DAYS	CLINICAL CONDITION*	BLOOD SUGAR IN MG. PER 100 C.C.	BLOOD CO ₂ COMBINING POWER IN VOL. UNES PER CENT	BLOOD NONPROTEIN NITROGEN IN MG. PER 100 C.C.	ORAL TEMPERATURE IN DEGREES FAHRENHEIT	RHYTHM	RATE	P-R INTERVAL IN SECONDS	Q-RS INTERVAL IN SECONDS	T-WAVE IN LEAD I	T-WAVE IN LEAD II	T-WAVE IN LEAD III	ELECTRICAL AXIS	REMARKS ON ELECTROCARDIOGRAM
1	7	Good	140	Not recorded	31	98.6	Normal rhythm	94	0.12	0.08	Up	Up	Up	Normal	High skin resistance
2	8	Good	80	Not recorded	Not recorded	98.4	Normal rhythm	90	0.16	0.08	Up	Up	Up	Normal	High skin resistance
3	3	Good	120	Not recorded	Not recorded	99.2	Normal rhythm	85	0.14	0.08	Up	Up	Up	Normal	High skin resistance
4	1	Good	330	10	66	101	Sinus tachycardia	130	0.16	0.08	Up	Diphasic	Inverted	Normal	High skin resistance
5	2	Good	80	29	72	98.6	Normal rhythm	94	0.16	0.08	Diphasic	Diphasic	Inverted	Left	
6	Died after two days of otitis media and streptococcus meningitis. Autopsy.						Normal rhythm	92	0.16	0.09	Inverted	Diphasic	Diphasic	Normal	High skin resistance
7	3	Good	70	32	39	100	Normal rhythm	92	0.16	0.09	Inverted	Diphasic	Diphasic	Normal	
8	2	Good	180	29	Not recorded	99	Normal rhythm	86	0.14-0.16	0.08	Up	Up	Up	Normal	
9	Died after two days of sepsis. No autopsy.														
10	Died on day of admission, of coma. No autopsy.														
11	No follow-up record obtained.														
12	2	Good	80	Not recorded	Not recorded	98.4	Normal rhythm	88	0.16	0.08	Up	Up	Flat	Normal	Slightly high skin resistance
13	2	Good	80	21	Not recorded	98.6	Normal rhythm	94	0.16	0.06	Up	Up	Flat	Normal	
14	2	Good	380	12	28	99	Sinus tachycardia	109	0.16	0.08	Flat	Low	Flat	Left	
15	2	Good	280	21	Not recorded	99	Normal rhythm	86	0.16	0.06	Up	Up	Flat	Normal	

*In all cases examination of the heart was recorded as negative except in Case 15 in which it was noted that the heart sounds were "distant."

level of nonprotein nitrogen in the blood of some cases of diabetic coma might therefore exert an effect of its own on the electrocardiogram.

Low Blood Pressure.—The blood pressure is often, though not constantly, lowered in diabetic coma, occasionally to such a degree that it is unobtainable by the usual auscultatory method.¹² This with other evidences of stagnation in the peripheral capillary bed might lead one to question whether there might not be similar changes in the myocardial circulation which would have an effect on the electrocardiogram.

PROCEDURE

Electrocardiograms have been taken immediately on admission in fifteen cases of diabetic coma at the New England Deaconess Hospital. Control electrocardiograms after emergence from coma were taken in eleven of these cases, from one to eight days later. Of the remaining four cases, three patients died and one left the hospital before a control record was taken. The clinical and laboratory data are summarized in Tables I and II. All of the cases were uncomplicated except Cases 5, 6 and 9 in which there were respectively hemochromatosis, streptococcus septicemia and sepsis. The patients varied in age from thirteen to forty-nine years, but only two were over forty years. There were eight females and seven males.

Clinically, the cases varied in severity from marked drowsiness to the most profound coma. The degree of acidosis as measured by the CO₂ combining power of the blood was ten volumes per cent or below, in seven of the thirteen cases in which it was recorded. The blood sugar levels ranged from 0.18 to 0.88 grams per 100 cubic centimeters. The nonprotein nitrogen of the blood was elevated above 35 milligrams per 100 cubic centimeters in nine of the fourteen cases in which it was recorded, the highest being 77. Fever was present in two cases (100° F. and 101° F. rectal respectively) and the body temperature was subnormal in five cases (95° F. to 97.2° F. rectal). The systolic blood pressure measured 100 milligrams Hg or below in seven cases. There were no cases of hypertension. Physical examination of the heart was negative in all cases except one in which it was noted that the heart sounds were distant.

ELECTROCARDIOGRAMS

All of the records were taken by means of a string galvanometer type of electrocardiograph, some being taken with a Hindle and the remainder with a Sanborn apparatus. An obstacle to precise analysis of the records taken during coma was presented by the high skin resistance which was uniformly present in these cases. The increased resistance was attributed to the low skin temperatures and the dryness of the skin. Efforts to overcome this by brisk scrubbing of the skin and application of hot water bottles were not successful. The resistance was still high in six of eleven cases in which the electrocardiogram was repeated after the coma had

cleared. In only one case, however, was the resistance high enough to interfere seriously with the interpretation of the ventricular complexes. The effect of high resistance in the circuit is to cause overshooting, with consequent exaggeration of the amplitude of individual complexes and sometimes to change a monophasic into a diphasic wave or to cause the T-wave to "take off" above or below the base line. In the presence of high resistance, therefore, one must be extremely cautious in interpreting abnormalities in the electrocardiogram. On the other hand, if the record is normal in spite of high resistance, one has only to discount a slight exaggeration in the amplitude of the deflections.

Of the fifteen records taken during coma all showed a sinus tachycardia; nine were otherwise completely normal. In two records the only abnormality was a diphasic T-wave in Lead II, and in one the T-waves were diphasic in both Leads I and II. In one case (Case 9) the T-wave in Lead II was of low amplitude, and there was slightly low origin of the T-wave in Lead I. In another (Case 12) the T-wave was flat in Lead I and low in Lead II. The decreased amplitude of the T-waves in these last two cases cannot be explained on the basis of high skin resistance. In Case 9 the patient died without regaining consciousness so that a control record was not obtained, but in Case 12 the control record showed normal T-waves. In three cases (Cases 5, 7 and 13) the opposite effect was observed, upright T-waves during coma, changing to flat, inverted or diphasic waves in the control record. No explanation is offered for this. It is of some interest that in Case 5 the patient died two months later from coronary thrombosis.

SUMMARY AND CONCLUSION

Electrocardiographic records have been taken in fifteen cases of diabetic coma. High skin resistance, which was uniformly present, offered a serious obstacle to precise analysis of the individual complexes. In nine cases the electrocardiogram was within normal limits, while in four others the abnormal feature (diphasic T_1 or T_2 or both) might be explained by "overshooting" due to the high skin resistance. In two cases the abnormalities could not be explained entirely on this basis. One showed a slightly low origin of the T-wave in Lead I with a low amplitude of T_2 . The other showed a flat T_1 and low amplitude of T_2 . Control electrocardiograms were obtained in eleven cases after emergence from coma. Of the four cases showing diphasic T-waves during coma, control records were obtained on two. One of these, in which high skin resistance persisted, still showed a diphasic T-wave in Lead II. The other, with normal skin resistance, gave a normal record. Of the two cases showing definite intrinsic electrocardiographic changes during coma, one patient died and the other gave a normal control record. Three cases with normal records during coma showed diphasic, flat or inverted T-waves in the control record.

The conclusion to be drawn from these cases is that electrocardiographic changes are not the rule in diabetic coma, and when present they consist

of minor T-wave abnormalities which are not likely to be confused with or to mask the picture of coronary occlusion.

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TRICUSPID STENOSIS

REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH ANTEMORTEM DIAGNOSIS*†

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ACQUIRED chronic fibroplastic tricuspid stenosis is sufficiently rare to warrant reporting a case, especially if the diagnosis was made during life and confirmed at autopsy. While far from unknown this condition is rare enough to be neglected in many textbooks. Asehoff¹ and Henke and Lubarsch² make no mention of it; while Kaufmann³ is content with saying that organic changes of the tricuspid valve are "vanishingly rare." Wiggers⁴ does not mention it at all, and Strümfell and Seyfarth⁵ say it is so rare as to have no practical importance.

FREQUENCY

Leudet⁶ reviewed the literature to 1888 and was able to collect 114 cases. J. B. Herrick⁷ reported three cases in 1897, bringing the total at that date to 154. W. W. Herrick⁸ reported one case in 1908, bringing the total to 187. Futeher⁹ reported five cases in 1911, total 195. Cottin and Saloz¹¹ reported one case in 1920, Oigaard¹² one in 1923, Hiller¹³ one in 1925, Dressler and Fischer^{14, 15} thirty in 1929 and three more in 1930, the Massachusetts General Hospital¹⁶ one in 1930. Cabot¹⁷ records thirty-three cases out of four thousand necropsies done at the Massachusetts General Hospital between 1896 and 1919; how many of these occurred before 1911 and were therefore presumably included in Futeher's review I do not know, but it is probably a fair estimate that not more than twelve of the thirty-three cases fall in the last eight of the twenty-three years. White¹⁸ stated in 1927 that Levine said he had recently seen three cases, but no other reference to these was found. Tschilikin¹⁹ refers to some observations of his in the Russian literature,²⁰ which I have not seen.

A study of the world literature to date has revealed only 232 cases of acquired tricuspid stenosis; if we include three cases of Levine, twelve of the Massachusetts General Hospital, and several of Tschilikin the total is increased to 250. Considering the enormous number of autopsies performed throughout the world this is a very low incidence, even lower than that indicated by its occurrence only seven times in 24,000 cases at the Johns Hopkins Hospital.²¹

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FREQUENCY OF DIAGNOSIS

The diagnosis of acquired tricuspid stenosis is usually not correctly made during life. Vaquez²² says it is "difficult of diagnosis"; Norris and Landis²³ say the diagnosis "cannot be made with any certainty"; Mackenzie²⁴ says that in the majority of cases it is not recognized during life. In Leudet's⁶ series of 114 cases the diagnosis had been correctly made *intra vitam* in only six. In the first 187 cases⁸ it was made in ten, in the first 195 it was made in thirteen. In Henschen's¹⁰ fourteen cases it was not made at all. Cabot¹⁷ says, "Looking back over the whole thirty-three cases of this complicated group one sees that, *though the tricuspid valve was involved in every one of them we only suspected this disease in one out of the thirty-three and did not even consider it in the others. . . .* Tricuspid lesions we practically *do not recognize at all.*" Dressler and Fiseher^{14, 15} report a series of thirty-three cases; of the first nineteen the diagnosis was made in only three, and of the last fourteen it was missed in only three. Aside from their cases the diagnosis has been made in only seventeen out of 217 cases, including Levine's¹⁸; altogether the diagnosis has been made in thirty-one out of the 250 cases so far recorded.

CLINICAL ASPECTS

The clinical aspects of tricuspid stenosis are very well discussed by J. B. Herriek⁷ and by Dressler and Fiseher.¹⁴ Only a few points in the symptomatology will be mentioned here. Dyspnea on exertion is practically always present if the lesion is advanced. Cyanosis is often, probably usually, present; while it may be very marked, it often is not.²³ There is always dilatation of the right auricle, with enlargement of the heart to the right. There is usually distention of the cervical veins, though this may not be great, and there is presystolic pulsation, of these veins with a large *a*-wave in the phlebogram. There is usually marked enlargement of the liver, with positive presystolic liver pulsation, detectable by palpation and by a liver pulse tracing. Auscultation of the heart must be very carefully performed, inasmuch as there is almost always a concomitant mitral stenosis, the signs of which often obscure those of the tricuspid stenosis. The mitral stenosis produces a presystolic or diastolic rough murmur at or near the apex, and the tricuspid stenosis a similar murmur at the xiphoid end of the sternum or just to the left or occasionally to the right of this point. The tricuspid murmur is often absent or indistinct,^{21, 22} and even if present may be obscured by merging indistinguishably into the mitral murmur.^{21, 22, 25} There may be two regions at which the murmur is at a maximum, one at the apical and one at the xiphoid region,^{22, 25} with decreased intensity or even absence of the murmur between, or the two

murmurs may differ slightly in character, thus facilitating the diagnosis. The pulse is usually small. There may or may not be polycythemia.

If the right auricle fails completely or if there is auricular fibrillation, then the signs dependent upon auricular activity are absent, namely the presystolic (but not the diastolic) murmur, and the presystolic pulsations of the cervical veins²⁶ and the liver.

CASE REPORT

D. M., a white boy aged fifteen years, came to the cardiac department of the Mandel Clinic on September 14, 1932, complaining of dyspnea on walking a short distance and of moderate cough with bloody sputum. He had been reported in



Fig. 1.—Distant heart plate, showing marked enlargement to the right and complete filling of the waist line.

good health by a camp physician in the summer of 1931 and had been apparently quite well until October, 1931, when he first noticed the above-mentioned symptoms. In December, 1931, he was told he had heart trouble. He was in bed from that time until July, 1932; during which interval he had been in two hospitals, had become weak, and had for some time had fever and marked edema of both legs. He left the hospital on July 22, 1932, with the diagnosis of rheumatic heart disease, mitral stenosis and insufficiency, enlarged heart. He had had scarlet fever and diphtheria in infancy, and measles and mumps later; the tonsils had been removed twice.

On September 14, 1932, the findings were as follows: The boy was thin, pale, and somewhat cyanotic. The cervical veins were somewhat full, and they pulsated visibly though only slightly. The lower right anterior chest and the right hypochondrium bulged somewhat, corresponding to the liver, which was felt 9 cm. below

the right costal border, down to the level of the umbilicus. There was slight but definite expansile pulsation of the liver, and pressure on the liver was accompanied by increased filling of the cervical veins. There was no pitting edema anywhere. The lungs seemed normal. Temperature was 98 degrees, pulse 104 and regular. Blood pressure was 136/74 mm. There was a presystolic thrill at the apex. The heart borders were 6 cm. to the right and 10.5 cm. to the left of the midsternal line, and the left border was straight. There was a rough presystolic murmur at the apex and also just to the left of the lower end of the sternum, while between these points the murmur was much less intense. There was a loud systolic murmur over the lower part of the heart. The second pulmonic sound was greatly accented. The boy was sent to Michael Reese Hospital with the diagnosis of chronic and subacute rheumatic myocarditis, mitral stenosis and leak, tricuspid stenosis and leak, hypertrophy and dilatation of the right ventricle and of both auricles, chronic passive hyperemia of the lungs and the liver.

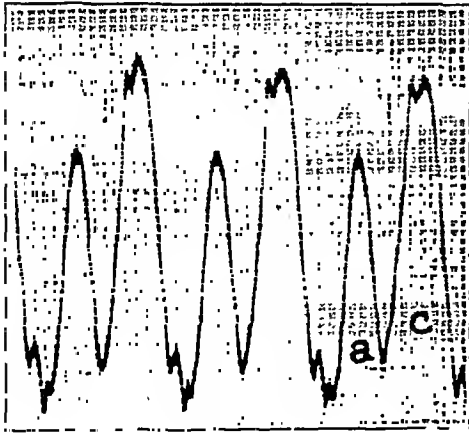


Fig. 2.



Fig. 3.

Fig. 2.—Simultaneous electrocardiogram and cervical phlebogram, showing very high α -wave.

Fig. 3.—Electrocardiograms with simultaneous liver pulse tracing (A) and heart sounds (B).

During his stay in the hospital the boy developed edema of the lower extremities and the back, and ascites. At one time he had sharp pain, aggravated by respiration, in the left precordial region. The hemoptysis continued. Two days before death there were decreased resonance, suppressed breathing, and râles over most of the right and the lower half of the left lung fields. He died on November 16, 1932. During his last stay in the hospital there was occasional slight fever. The urine contained albumin but no erythrocytes. Two blood cultures showed non-hemolytic streptococcus, and a third was negative. A cervical phlebogram showed a high α -wave (Fig. 2), and a liver pulse tracing showed a presystolic wave* (Fig. 3). The final clinical diagnosis was as above with the addition of marked dila-

*These tracings were taken by Dr. Anne Bohning.

tation of the right auricle, intra-auricular thrombns, repeated pulmonary emboli with infarets, marked heart muscle failure, anasarea, hydrothorax, ascites.

Autopsy was performed by Dr. Otto Saplir on the day of death. Both lower extremities were markedly edematous. The abdomen bulged. The skin and sclerae were slightly yellowish. Each pleural cavity contained about 700 c.c., the peritoneal cavity about 1500 c.c. of clear liquid. The heart was markedly enlarged and distended, weighing 625 grams. At the roots of the large vessels there were a few adhesions between the two layers of the pericardium. There were a few thrombi attached to the mural endocardium of both auricles. The endocardium in the region of the left ventricle corresponding to the interventricular septum was white and thickened. There was a small endocardial pocket, open toward the aortic valve, in about the midportion of the interventricular septum. The mitral valve leaflets were much thicker than normal, shrunken, and fused by confluence. The chordae



Fig. 4.—View of the narrowed tricuspid orifice from above.

tendineae were thickened, and many of them fused. The orifice of the mitral valve was only 4.2 cm. in circumference, much smaller than normal. The line of closure was studded with a row of beadlike vegetations. The aortic valve leaflets were somewhat thicker than normal; they were a little shrunken in the longitudinal diameter, but there were no adhesions between the cusps. The pulmonary valve was normal. The leaflets of the tricuspid valve were much thicker than normal, shrunken, and fused by confluence. Its orifice was only 7.1 cm. in circumference (Figs. 4 and 5). The coronary arteries were normal. The papillary muscles and the columnae carneae were thickened and flattened. The right ventricular wall was 4 mm. thick, the left 12 mm. The hypertrophy of the right ventricle was much more pronounced than that of the left. The right auricle was greatly dilated and its wall thickened up to 3 mm. Cut surfaces exposed by cutting the myocardium were gray, and showed several lighter gray and whitish spots and streaks. Histological examination of the myocardium revealed a marked increase in connective

tissue, in some places with hyalinization of the connective-tissue fibers. A very few sections revealed an infiltration of cellular elements (endothelial cells and occasional lymphocytes) in the perivascular spaces. In some fields these cells were in parallel rows suggesting Aschoff bodies.

The lower lobe of the right lung showed an organizing bronchopneumonia. In the left lower lobe there was a hemorrhagic infarct, and a branch of the pulmonary artery within this area was blocked by an embolus; there was a similar area in the right middle lobe. The liver was large and firm, weighing 1650 gm., and the seat of very marked passive hyperemia, with fatty changes. The spleen was enlarged, 600 gm., and firm. There were several yellow, wedge-shaped infarcts in the spleen. There was passive hyperemia, and there were several infarcts in the kidneys.



Fig. 5.—View of the narrowed tricuspid orifice from below.

DISCUSSION

Heart muscle failure with pronounced edema in this boy of fifteen years suggested strongly the presence of some abnormality besides mitral stenosis, inasmuch as cardiac edema in a child of this age is unusual. The most likely lesions were adhesive pericardiomediastinitis and a tricuspid lesion. There were no signs of the former, such as Broadbent's sign, inspiratory filling of the cervical veins, diastolic apical shock, fixation of the heart. Consequently we strongly suspected a tricuspid lesion. The enormous enlargement of the right auricle, and the pulsation of the cervical veins and the liver supported this opinion,

though without knowing the time of the pulse-waves the diagnosis of stenosis was not warranted.

The configuration of the heart and the murmurs confirmed the diagnosis of mitral stenosis. The presence of a presystolic rumble in the tricuspid area suggested tricuspid stenosis but did not prove it, inasmuch as the apical murmur in mitral stenosis may occasionally be transmitted to the sternum. But the almost complete absence of the murmur between the apex and the tricuspid area strongly indicated that the murmurs at those two areas were distinct and not due to one lesion.

SUMMARY

1. A review of the world literature to date reveals 250 cases of acquired chronic fibroplastic tricuspid stenosis, with correct ante mortem diagnosis in only 31.

2. The most important symptoms and signs of tricuspid stenosis are: Dyspnea on exertion, cyanosis, dilatation of the right auricle, distension of the cervical veins, presystolic pulsation of the cervical veins with a large *a*-wave in the phlebogram, marked enlargement of the liver with positive presystolic liver pulsation, a rough diastolic and presystolic murmur at the xiphoid end of the sternum. Those signs dependent on auricular activity disappear in auricular fibrillation or complete failure of the right auricle.

3. A case of tricuspid stenosis is reported, with correct ante mortem diagnosis, confirmed by autopsy.

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APPARATUS FOR THE DETERMINATION OF VENOUS PRESSURE IN MAN*

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VENOUS pressure is obtained in man by two methods, the direct and the indirect. The technic of the direct method requires the inserting of a large needle or trocar into a superficial vein of the forearm, and the connecting of the column of blood directly with a manometer upon which the pressure is read. The factors that make this procedure impracticable are the necessity of a sterile technic, possibility of the blood clotting, trauma to the vein, pain and other objections of the patient, and the inability to make repeated pressure determinations.

The indirect method depends upon the principle that the least pressure applied outside a vein required to actuate collapse will be practically equal to the pressure within the vein. Numerous instruments having either a water or a mercury manometer have been devised for this purpose, but they are expensive and repairs are difficult. The use of the water manometer is the most suitable, but the reading is hard to obtain because the column of water fluctuates to such a marked degree while pressure is being applied over the vein.

CONSTRUCTION

These objections have prompted the presentation of a modified apparatus for the determination of venous pressure in man by the indirect method. It consists of an ordinary thistle tube (1), over which has been tightly stretched a piece of a rubber glove (2), which has a small opening in its center (3), and is held taut and in place by a rubber band (4). The thistle tube is connected by rubber tubes and a T-tube (5) to a water manometer (6) and an ordinary rubber blood-pressure cuff (7). A pressure bulb (8) with an escape valve (9) is attached to the other opening of the rubber bag or cuff. The construction of the manometer is a glass tube bent in a manner (13) so as to have one end close to the bottom of a small glass reservoir (11). The manometer tube is connected to the reservoir through one of two openings in a rubber stopper (12), while an L-tube (10) through the other connects with the rest of the apparatus. The manometer tube and the reservoir are mounted upon a base board beside a meter stick (14). After the reservoir and the curved end of the manometer tube are partly filled with colored water, the meter stick is adjusted so that 0 is opposite the level of the water in the long arm of the tube. If the fluid level is a short distance above this point, the number of millimeters can be subtracted from the pressure reading.

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METHOD

The patient is placed in a semi-recumbent position with the right arm extended so that the hand is brought to a level with the right auricle of the heart. A large superficial vein of the hand is selected and surrounded by a ring of vaseline or water soluble jelly. The thistle tube is placed against the hand in such a manner that the opening in the rubber diaphragm is directly over the vein. In this position the vein can be watched through the glass thistle tube while air is pumped in by means of the pressure bulb. The reading is made in millimeters on the meter stick the instant the vein is collapsed.

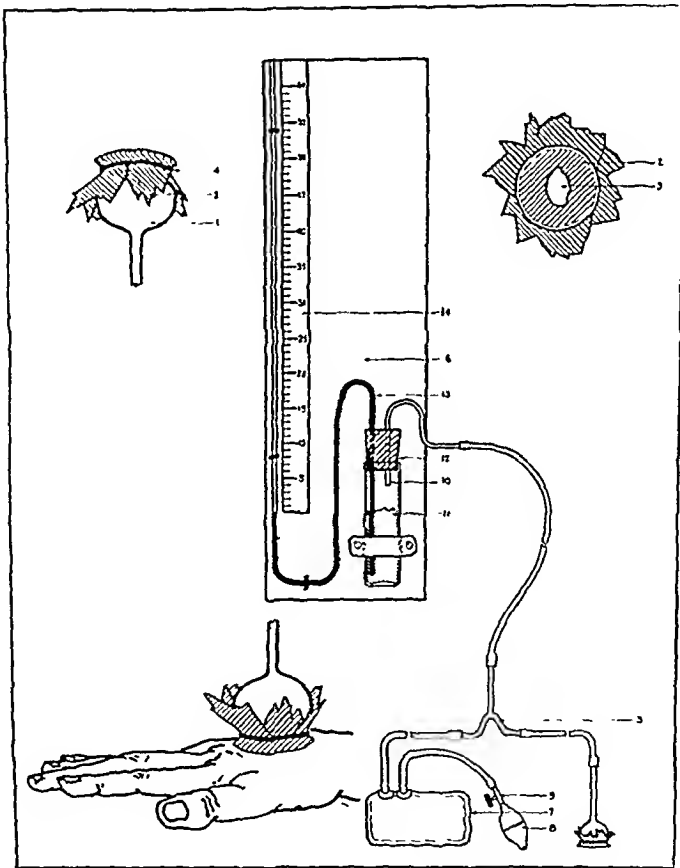


Fig. 1.—Diagram of venous pressure apparatus.

DISCUSSION

This instrument is inexpensive and can be made in any laboratory without requiring mechanical skill. The rubber bag or cuff acts as a buffer and allows the water to rise slowly and evenly in the manometer tube, thereby facilitating the ease and accuracy of the reading. The apparatus can be easily and rapidly repaired without requiring expensive parts. The apparatus is made portable by draining the water from the tube and the reservoir and refilling at the bedside.

DIGITALIS ASSAY WITH THE ISOLATED CAT HEART, COMPARED WITH OTHER METHODS*†

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WE HAVE used the simplified heart-lung preparation¹ of the cat for the bio-assay of 8 different preparations of digitalis bodies, and compared the potency, determined in this way, with the "pigeon-emetic" potency of the same preparations, the "pigeon-fatal" dose (6 preparations), as well as with the dose for the intact cat, and for the frog (5 preparations).

METHODS

Cat heart-lung preparations were made by ligating the azygos vein, the superior vena cava and the carotid and subclavian arteries of cats anesthetized with ether and given artificial respiration through a tracheal cannula. The inferior cava was occluded with a bull-dog clamp and the aorta by a hemostat at the level of the left subclavian artery. Blood was admitted into the heart from the inferior cava until the left auricle was full, but not distended, and the aorta pulsated strongly. Once the heart volume was satisfactory, the hemostat and the clamp on the inferior cava were not touched, and the volume of blood in the isolated circuit remained constant. Such preparations, kept at room temperature, lasted for two to five hours, and almost as long when kept at 37° C. The digitalis preparations, suitably diluted with 0.85 per cent NaCl solution, were injected with a tuberculin syringe and fine hypodermic needle into the left ventricle. Injections were made at five-minute intervals, beginning with 50 to 70 per cent of the estimated fatal dose and giving 10 per cent more at each injection. Ventricular fibrillation with persisting dilatation was taken as the end-point. It was noted that auricular stand-still, due to sino-auricular and nodal auricular block, occurred before ventricular fibrillation, usually after 70 to 90 per cent of the fatal dose. Ectopic ventricular beats occurred less often and were less striking.

"Pigeon-emetic" and "pigeon-fatal" doses (on intravenous injection) were determined in the usual way,² using groups of 7 pigeons for the final assay with doses 10 per cent \pm the emetic dose, and 5 pigeons for the final assay of fatal doses. Thus, 20 to 25 pigeons were used for each emetic assay, and 12 to 15 for the fatal dose.

RESULTS

It was found that twice the fatal dose of strophanthin caused arrest of the isolated heart in forty to fifty seconds, while twice the fatal dose of digitoxin arrested the ventricles in one hundred and twenty to one hundred and fifty seconds. It was therefore considered proper to space injections at five-minute intervals. When assayed at 37° C. instead of

*Supported, in part, by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University.

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TABLE I
RESULTS OF BIO-ASSAY, USING VARIOUS METHODS

Maximum and minimum values for the 8 cats used in each assay are given in italics, average values in roman type. The ratios of emetic (E) to isolated heart (C) dosages, of pigeon-fatal (F) to isolated heart and to emetic doses are given.

PREPARATION	ISOLATED HEART DOSE PER KG. CAT MG. PER KG. C	ISOLATED HEART DOSE PER GM. HEART MG. PER KG.	PIGEON- EMETIC DOSE MG. PER KG. E	PIGEON- FATAL DOSE MG./KG. F	RATIO E/C	RATIO F/C	RATIO F/E
<i>Digitalis purpurea</i> tincture, Hatcher cat unit = 108 mg.	9.5 <i>7.2 to 12</i>	3.1 <i>2.1 to 4.3</i>	25.00	142.00	2.6	15.0	5.7
<i>Digitalis lutea</i> (an old tincture)	9.5 <i>7.4 to 11.7</i>	3.0 <i>2.4 to 3.9</i>	15.00	60.00	1.6	6.3	3.0
<i>Digitalis purpurea</i> (an old tincture)	16.0 <i>13.0 to 20.0</i>	5.0 <i>3.8 to 6.4</i>	40.00		2.5		
Digitoxin (Merck)	0.10 <i>0.071 to 0.15</i>	0.030 <i>0.022 to 0.044</i>	0.21	0.40	2.1	4.0	1.9
Strophanthin K	0.020 <i>0.017 to 0.024</i>	0.0065 <i>0.0053 to 0.0078</i>	0.04	0.20	2.0	10.0	5.0
Scillaren A	0.019 <i>0.0141 to 0.024</i>		0.03	0.43	1.6	23.0	14.0
Scillaren B	0.019 <i>0.013 to 0.022</i>		0.05	0.20	2.7	11.0	4.0
Scillaren, total glucoside	0.017 <i>0.043 to 0.087</i>		0.09	0.20	5.31	12.0	2.2
Digitoxin, 37° C.	0.055	0.018					
Strophanthin, 37° C.	0.016 <i>0.0151 to 0.0161</i>	0.005					

at room temperature, digitoxin was 82 per cent more active, strophanthin 25 per cent more active. The variation in dose per gram of heart was greater than that per kilogram of cat, due to the greater sensitivity of enlarged hearts to these drugs.³ The variation between maximum and minimum dose per kilogram of 8 cats used for each preparation was 202 per cent in one group, but averaged only 68 per cent. This is distinctly less than the variation in groups of this size using the Hatcher

TABLE II

RELATIVE POTENCIES INDICATED BY DIFFERENT METHODS OF ASSAY. THE POTENCY OF DIGITOXIN FOR ANY ASSAY METHOD IS TAKEN AS 1

METHOD OF ASSAY	DIGITOXIN PER MG.	FOLIA DIGITALIS PER GM.	K-STROPHANTHIN PER MG.	SCILLAREN A PER MG.	SCILLAREN B PER MG.
Isolated cat heart at room temperature	1.0	10.5	5.00	5.3	5.3
Pigeon-emesis	1.0	8.4	5.25	7.0	4.2
Frog	1.0	7.1	4.00	4.0	6.7
Hatcher cat	1.0	3.6	2.00	1.35	2.0
Pigeon-fatal	1.0	2.8	2.00	0.90	2.0
Therapeutic for man	1.0	1.5			

method (whole cat). The results of all assays made by us are summarized in Table I; the relative potencies indicated by our assays and those of others in Table II.

COMPARISON OF VARIOUS METHODS OF ASSAY

The relative potency of digitalis bodies, assayed by various procedures, is given in Table II. The figures for frog and Hatcher cat doses were taken from Rothlin⁴ and Fromherz;⁵ those for the therapeutic dose for man from Eggleston.⁶ It is obvious that two main groups of results are shown. One group (isolated cat heart at room temperature, "pigeon-emesis," frog) indicates that digitoxin is relatively weak in comparison with total digitalis glucoside and the glucosides from strophanthus and squills. The other group (intact cat, "pigeon-fatal") indicates that digitoxin much more closely approaches the other substances in potency. The therapeutic dose for man not only falls in the second group, but is most strikingly at variance with the results of assay by the first three methods.

A number of factors may account for the difference in potency of digitoxin and the other preparations when assayed by these methods. In the isolated heart, injected at five-minute intervals, the relative speed of fixation by the heart of digitoxin and of other glucosides is obviously important. The fixation of digitoxin is known to be accelerated as temperature rises. The differences between assay with cold preparations (isolated heart at room temperature, frog) or preparations in which the period of assay is short (isolated heart at 37° C.) and assay with slower or warmer preparations, might be due entirely to relative speed of fixa-

tion. At room temperature, strophanthin is fixed more than twice as rapidly as digitoxin, but even so, when the interval between injections is twice as long as needed for 50 per cent fixation and the initial dose is 50 to 70 per cent of the final dose, reached fifteen to thirty minutes later, it seems improbable that temperature and duration of the periods of assay can account for the differences in relative potency shown in Table II, although they undoubtedly play some part.

The difference in dosage for isolated hearts at 37° C. and intact cats points to differences in extracardiac fixation of the drug as one factor in causing differences in relative potency. The data in Table II suggest that digitoxin is fixed or destroyed by extracardiac tissues to a lesser degree than total digitalis glucoside, or the other glucosides tested, and further, that the fatal dose for the frog and emetic doses for pigeons are not affected by the extracardiac tissues. The intact frog, at room temperature, behaves much like the isolated cat heart as an indicator of digitalis potency.

The contrast between the "pigeon-emetic" assay and the "pigeon-fatal" dose assay is of great interest. In both tests digitalis bodies are injected into the vein of intact, warm birds, yet the fatal dose closely parallels the cat-fatal dose and the emetic dose parallels the dose for cold isolated cat heart, and diverges from the assay by killing pigeons or cats more even than does the frog assay. In these two pigeon methods, the rate of reaction of the various bodies with the tissues is of importance, for emesis occurs very promptly and, if it is to occur at all, does so within one to fifteen minutes. Death from average fatal doses occurs in five to sixty minutes after digitoxin, in five to ten minutes after strophanthin or scillaren. The average time is thirty-five minutes for digitoxin, seven minutes for the other glucosides. The period between injection and emesis, from average emetic doses, is eight and one half minutes for digitoxin; eight and three-tenths minutes for strophanthin, and the same or slightly longer for scillaren. Fromherz⁵ has reported that the dose of digitoxin for cats is only one-half as great if no time limit is set, as when ninety minutes is taken for the period of assay. He found that the maximum effect was three to four hours after injection. Whether or not this is confirmed for cats, it does not hold true in pigeons, for practically all birds which survive average or less than average doses for one hour recover. Rarely death occurs seventy to one hundred and twenty minutes after injection, but the time allowed for assay (sixty minutes) will include almost all birds which will die, and, like the time (fifteen minutes) allowed for emesis, it equals nearly twice the average time for effect of average doses. In spite of the striking difference between duration for effect of emesis and for fatal action which distinguishes digitoxin from the other glucosides, it seems to us highly improbable that rate of fixation accounts

for the difference in relative potency indicated by the two pigeon methods of assay when the period of assay is long.

The difference between the results of assay by emetic and by fatal effect on pigeon, when ample time is allowed for the effect of the slowest preparation to be manifest, can be due only to a fundamental difference between the sites at which the two effects are produced. It seems highly probable that the fatal effect, produced entirely by action on the heart, varies with the amount of drug fixed or destroyed in the other tissues, while the emetic action is unaffected by the relative fixation of the drug in cardiac and extracardiac tissues. The difference in potency, indicated by emetic assay as compared with that indicated by fatal effect, as well as the fact that digitoxin which produces emesis as rapidly as other preparations, kills five times more slowly, indicates very clearly that emesis does not arise as a reflex from glucoside action on heart muscle. If it is of reflex origin, it probably arises from nerve endings wherever digitalis glucosides are taken up by the tissues and is unaffected by the speed or degree of cardiac absorption of the drug.

The fact that different methods of assay are not comparable was apparent in Eggleston's⁶ early study of the relatively high potency of digitoxin given orally to patients as contrasted with the effects of digitalis and digitoxin on cats. His findings are included in Table II. The difference between methods of assay has often been emphasized. Extensive data have been reported by Knaffl-Lenz⁷ and Fromherz⁸ has recently added further data on the assay of digitoxin, digitalis glucosides and derivatives on frogs and cats. He found that total digitalis glucoside was much more toxic for frogs than for cats, as compared with digitoxin, and suggested that the total glucoside must contain a substance toxic for frogs but not for cats.

He found that a pure glucoside, digitoxin, was much more toxic for frogs than for cats, as compared with another pure substance, gitoxin. One cat unit of gitoxin equalled 50 frog doses, one cat unit of digitoxin equalled 100 frog units, and one cat unit of total glucoside equalled 150 frog units. Our assays with isolated cat hearts, and with pigeons, show that digitalis total glucoside, tested on one species, may be 2 or 3 times more potent in comparison with digitoxin by one method of assay than another. Such differences cannot be explained by species difference, and the facts brought out by this paper, as well as those by Fromherz, can only be explained by differences in site of action and fixation.

The differences in action of different bodies, such as scillaren, strophanthin, and digitoxin, have long been recognized; and it was clear that assay could be used only for controlling potency of products, not for predicting action in other assay methods or in clinical use. Even with preparations made by similar methods from a single species of plant, very different relative potencies may be indicated by different

methods of assay. Thus Hanzlik² had reported that the "pigeon-fatal" dose of one tincture was 2.6 emetic doses, that of another tincture 12 emetic doses. In Table I, one tincture of digitalis had identical effects, on isolated cat hearts, with another tincture, but the "pigeon-fatal" dose of one was 2.4 times that of the other. While some attempts to correlate assay by experimental methods with assay on man have been made, most of these are inadequate. Either too few patients were used, or the criteria of effect were not sharply drawn, or the different substances tested were too closely related in potency and had been assayed only by a single method. To be truly informative, clinical assay should be made with two substances, whose relative potency, measured by one method of bio-assay, differs from that given by another method. Eggleston's studies show that cat assay and therapeutic assay agree for infusions and tinctures of digitalis, but not for tinctures or infusions and digitoxin. In connection with the League of Nations Hygiene Organization, studies of the potency of three lots of folia digitalis were made in many laboratories and in two clinics.⁷ In clinical assay by Gilchrist and Lyon⁸ 99 trials were made on cases of auricular fibrillation, and 15 on one patient. The general results and those on one patient agreed in assigning relative potencies as follows—A:65; B:90; C:100. The assays on frog (*Rana temporaria*) averaged as follows—A:50; B:94; C:100; those on other frogs, A:54; B:105; C:100. Infusions on cats gave—A:60; B:115; C:100; and tinctures tested on cats gave A:62; B:100; C:100. In other words, cat assay agreed with clinical assay about as closely as did frog assay. If, in Table II, the relative potency of digitoxin and that of digitalis leaf are compared, it is evident that the cat and "pigeon-fatal" doses parallel clinical effects, and the "pigeon-fatal" dose is more nearly parallel to clinical doses than any other.

The object of bio-assay is to permit the potency of drugs used in therapeutics to be maintained as nearly as possible at a constant level, and careful assay by any of the methods referred to in this paper, as well as several others, may be satisfactory for this purpose. The isolated cat heart, the "pigeon-emetic" method, and the frog method are more sensitive to differences in potency than are the fatal assays on pigeons or cats, or the therapeutic test on patients. Foxglove leaves of equal potency, assayed by any of these methods, will be closely related in their clinical potency. The choice of a method of assay would seem to rest largely on the ease and inexpensiveness with which many test animals can be used, for the accuracy of assay depends not merely upon carefulness but on the use of relatively large groups of animals.⁹ The pigeon methods are relatively inexpensive and rapid, and although, with digitalis leaf, the emetic dose parallels effect on man,¹⁰ it probably would be better to assay preparations for both emetic and fatal effects,

and to reject, for therapeutic use, preparations varying by more than 25 per cent from the standard in either type of assay.¹¹

SUMMARY

1. A method of assay using a simple heart-lung preparation of the cat for determining cardiac activity of digitalis bodies is described and compared with other methods of assay, particularly the emetic and fatal dose for pigeons.

2. There is strong evidence that, in pigeons, the emetic phenomenon is in no way related to the cardiac action of digitalis substances.

3. There is a close parallel between results of assay by isolated cat heart, frog, and pigeon emesis, and between assay by fatal effect on whole cats, or pigeons, and therapeutic effects on man.

4. Frog assay or pigeon emetic assay is more sensitive to differences in potency than is cat or pigeon fatal effect assay.

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Department of Clinical Reports

VENTRICULAR TACHYCARDIA, RATE OF 300, FOLLOWING THYROIDECTOMY

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THERE continues to be a difference of opinion concerning the origin of the cardiac impulse in cases with very rapid ventricular rates. Although the criteria for differential diagnosis are rather confusing in this case, we believe it to be one of ventricular tachycardia, with a rate faster than any heretofore published.

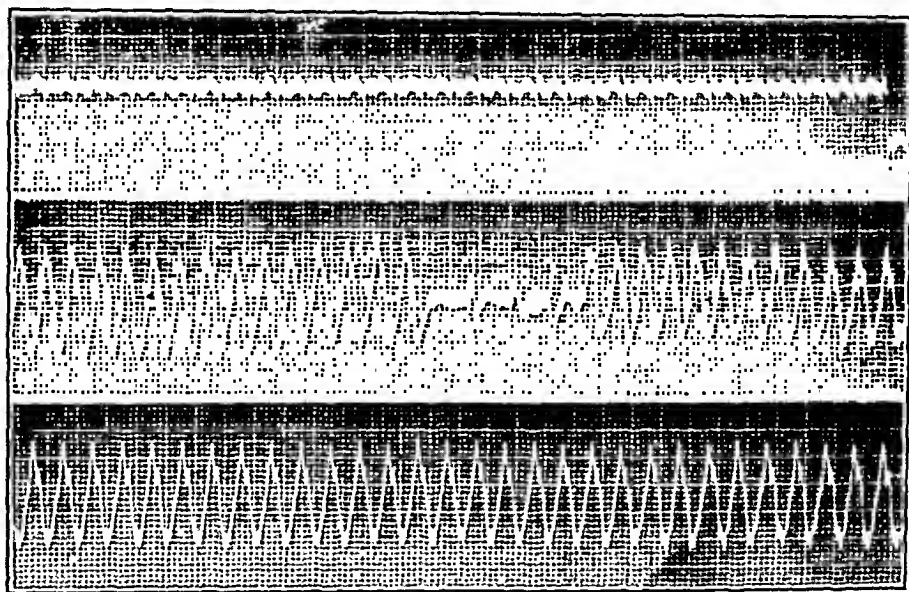


Fig. 1.—September 15, 1932. During paroxysm of ventricular tachycardia.

A white American male, aged fifty years, in 1930 complained of "nervous indigestion" and palpitation of the heart on exertion. He was advised at a clinic that his trouble was due to the mental strain connected with his occupation, and that he should have more relaxation in the open air to correct a spastic colon.

He first came under observation in June, 1931, complaining of troublesome gastrointestinal symptoms and of heart consciousness and palpitation, but no dyspnea, edema or cough. Emotional disturbances and exertion were about equal in producing his symptoms. He was accustomed to taking his own pulse and said that he had found it as high as 120. He had not lost weight. He had a tendency to watery stools and continued to have indigestion, whether he ate sparingly or forced himself to eat a rational diet.

The man was pale and extremely apprehensive. He had cold bluish hands and was perspiring profusely in the arm pits. His reflexes were all hyperactive. The heart was found to be normal, except for the rate, which was 92 per minute. The blood pressure was 170 mm. Hg systolic, 70 mm. Hg diastolic. This systolic hypertension, as well as the elevated pulse rate, was attributed to excitement and apprehension. There was practically no thyroid tissue palpable. The urine was normal. Blood examination

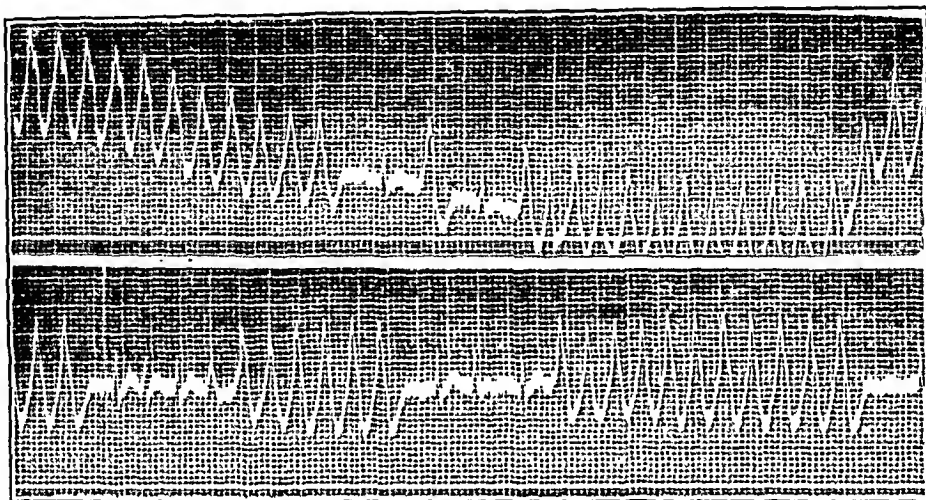


Fig. 2.—Lead II. Deep breath holding during paroxysm.

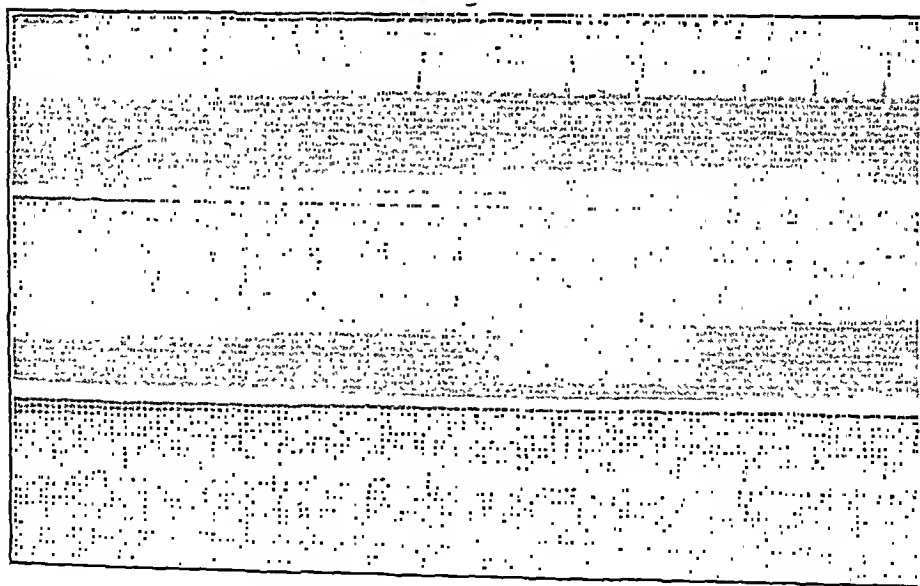


Fig. 3.—Auricular fibrillation twenty-four hours after paroxysm.

showed a hemoglobin of 70 per cent; R.B.C. 3,660,000; W.B.C. 6,550, with a normal differential count. The Wassermann test was negative.

On the second examination ten days later, the pulse rate was 76 and the blood pressure was 138-70. One month later the patient was greatly encouraged and regarded himself as well.

Four months later, October 21, 1931, at the insistence of an insurance company, an electrocardiogram was made which showed a rate of 70 and was essentially normal (Fig. 4).

On November 30, 1931, he came for reexamination complaining of a return of his former symptoms which he dated definitely to the day he received a letter from the insurance company saying that he had been refused insurance. His anorexia had returned. The gastrointestinal discomfort had reappeared, and he was unable to eat without being distressed.

In February, 1932, the patient was seen by a colleague. His complaints were all related to his gastrointestinal tract. After careful examination and repeated study this physician was of the opinion that the patient's cardiovascular system was not abnormal. Following this there was a remission of symptoms, the patient voluntarily stated that he felt better than he had for two years.

About six months later, September 1, 1932, the patient showed a marked and abrupt change in his condition without any known exciting factor. He became more nervous and apprehensive than he had ever been before and for the first time was tremulous.

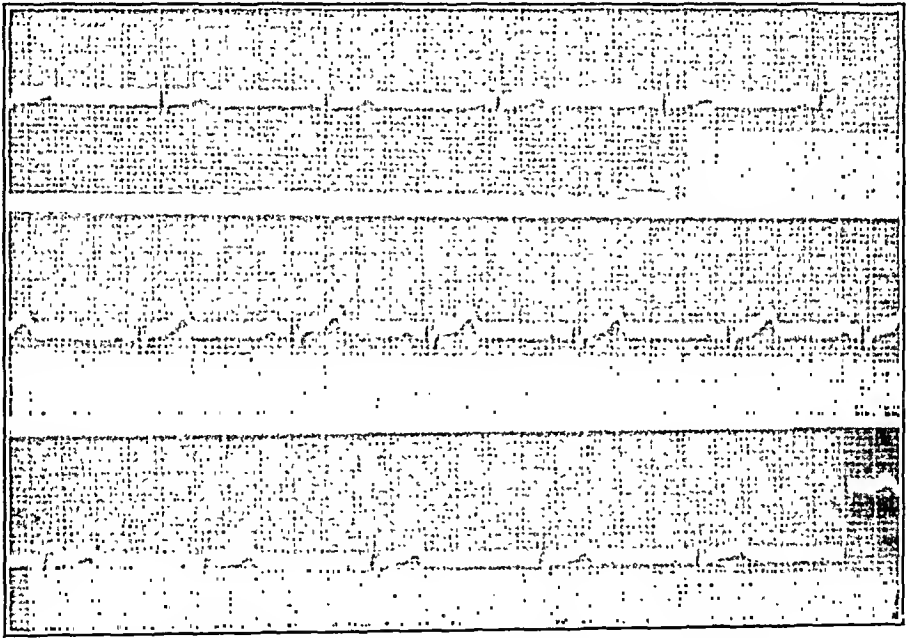


Fig. 4.—October 26, 1931. One year before thyroidectomy.

There was a continuously rapid pulse rate, a sharp weight loss, and a marked increase in basal metabolic rate (plus 43 per cent). The diagnosis of Graves' disease was then made.

A bilateral thyroidectomy was performed September 14, 1932, at 8 A.M. The pulse rate at operation varied between 110 and 120. Until thirty-six hours after operation his postoperative course was uneventful, except for the extreme apprehension, which seemed to be part of the personality make-up of this individual. The nurse recorded the pulse at 7:35 P.M. the day following the operation as 120. Ten minutes later the patient collapsed, and his pulse rate could not be counted. The skin was cold and clammy, and the blood pressure was unobtainable. Electrocardiograms were taken two hours after the onset of the attack. The patient at this time looked extremely ill. The pulse was almost imperceptible. The blood pressure was 60 mm. Hg systolic, 40 mm. Hg diastolic. The rate was so rapid as to be uncountable. The heart was pounding vigorously at a regular rhythm, interrupted at varying intervals from five minutes to less than a minute by short periods of a different rhythm. The pulse at the wrist during the short interruptions was more perceptible than during the prevailing

rhythm. The patient complained of discomfort in the chest and profound weakness. He was given morphine sulphate, gr. $\frac{1}{4}$ at 8:30 P.M. Pressure on the eyeballs and on the carotid sheath produced no change in rate or rhythm. Deep breath holding, which feat the patient was unable to perform very satisfactorily, produced more frequent interruptions in the prevailing rhythm and an increased rate. Six grains of quinidine sulphate were given at 10:15 P.M. At 1:00 A.M., about five hours after the onset of the tachycardia, the patient's condition seemed critical. There were signs of pulmonary edema. Quinine hydrochloride, $7\frac{1}{2}$ grains, was given intravenously. Immediately after the administration of this drug the rhythm changed to auricular fibrillation with a ventricular rate of about 150. He became very much better clinically and from then on improved rapidly. Within forty-eight hours the rhythm was normal. Quinidine sulphate, grains 4 twice a day, was continued for several days, as well as digitalis. The patient left the hospital in a wheel chair on October 3, 1932.

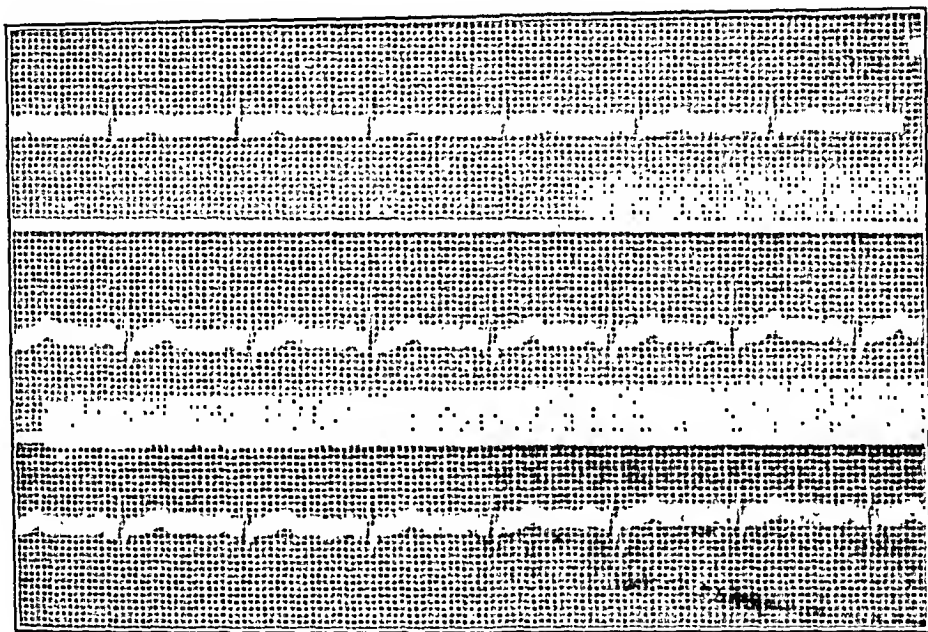


Fig. 5.—September 21, 1932. Normal rhythm one week after thyroidectomy.

DISCUSSION

The interruptions of the extremely rapid rhythm are supraventricular in origin and probably represent auricular fibrillation. During these periods of irregularity it will be noted that the ventricular rate continues to be about 250, beyond which rate, according to previously reported cases, the auricles and ventricles usually become dissociated. It is possible that the notching on the descending limb of the R-waves may represent auricular impulses to which the ventricle was able to respond up to the rate of 300, which if true would establish this as a case of auricular flutter with one-to-one conduction.

In favor of the ventricular origin of the tachycardia, however, is the undoubted ventricular characteristic of the complexes which dominate the picture and the prompt response to quinine therapy. In addition to this, the clinical observation that the pulse volume was much stronger

during the short periods of interrupted rhythm merits consideration, since premature ventricular contractions often fail to be palpable at the wrist. Furthermore, the frequent interruption of a prevailing rhythm is more characteristic of ventricular than auricular tachycardia. It is probable that the notching on the descending limb of the R-waves represents auricular beats produced by retrograde conduction of impulses from the ventricle to the auricle.

Scott's criteria¹ on ventricular tachycardia are difficult to apply in this case. He believes with Lewis² that the paroxysm starts abruptly and ends abruptly, and that to be of ventricular origin it must begin with a premature systole of ventricular origin and end with a diastolic pause comparable to that encountered after a premature systole. In our records the interruption of the prevailing rhythm did not occur in the same manner each time, nor did it recur following any constantly typical complex.

Wiggers³ states that "the only other way in which a ventricular tachycardia can be diagnosed with certainty is to establish that undoubted P-waves occur at a rhythm which is slower and unrelated to the ventricular beats." This does not seem to be true in this case.

The effect of deep breath holding during the paroxysm is interesting. The rate increased from 300 to 325. The type of QRS complex was definitely changed, and the periods of interruption were more frequent.

Mention should be made of the possibility that the palpitation from which this patient suffered in 1930 might have been due to hyperthyroidism. Certainly evidence sufficient to warrant operative interference was lacking until a few weeks before an unusual and almost fatal disturbance in the heart's mechanism occurred. It is interesting to note from serial electrocardiograms how completely the myocardium has recovered. Clinical data confirm this fact.

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COMPLETE HEART-BLOCK OF THIRTY YEARS' DURATION*

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THE diagnosis of complete heart-block usually conveys the idea of rather severe, diffuse myocardial injury, and in the majority of instances this impression is correct, especially if the complete auriculo-ventricular dissociation is the result of arteriosclerosis. Several cases of complete heart-block of rather long duration have been reported, and in several instances the heart-block has in no way interfered with the activities of the patients. In Ellis' series,¹ he reported one case of twenty-four years' duration, two of nine years' duration, and one of seven years' duration. None of these four patients had symptoms or any other evidence of any cardiac insufficiency. White⁴ reported two cases in which the patients had persistent, complete heart-block for fourteen and fifteen years respectively, and their heart-block had in no way interfered with their activities. In a series of thirty-seven cases of complete heart-block reported by Willius,⁵ the average duration of the history indicating auriculoventricular dissociation was two and nine-tenths years, and the longest duration was fifteen years. Willius⁶ also has reported a case, however, of twenty-two years' duration. Russell-Wells and Wiltshire³ followed a case of intermittent heart-block for twelve years, and the patient died of carcinoma of the cecum. Harris² reported a case in which complete heart-block had been present for twenty-eight years, and the patient had enjoyed good health during this whole period. Keith described a case in which there was a history of complete heart-block for eighteen years.

REPORT OF CASE

A white janitor, forty-three years of age, came to The Mayo Clinic complaining of rectal fistula and some shortness of breath on severe exertion.

At the age of thirteen years he had had an acute illness accompanied by extremely sore throat, and what apparently were bilateral retropharyngeal abscesses had been lanced. His temperature at that time had been as high as 103° F. He had been given diphtheria antitoxin; there were cases of diphtheria and scarlet fever in the neighborhood where he lived. His two sisters had been given prophylactic doses of diphtheria antitoxin at the same time. His physician had not been sure whether the patient had diphtheria or not. About one week after his acute illness had subsided his cardiac rate became very slow, and he again was confined to bed for several weeks. His pulse rate had been below 40 each minute at the time referred to, and had remained between 30 and 40 most of the time through all the subsequent years. Tonsillectomy had been performed about ten years before he came

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to the clinic, and his pulse rate had been slightly faster for a short time following the operation. He stated that after his spell of acute illness he would become short of breath on severe exertion. Because of this he could not run and play as well as other children could. While he was a child he had learned just how much he could do without getting short of breath. With severe exertion he would become light-headed and dizzy, although with moderate exercise he encountered little difficulty. As far as he was able to tell when he was examined at the clinic, his condition was no worse than it ever had been since his illness. He had never fallen nor lost consciousness.

The man was well developed and well nourished; he weighed 195 pounds stripped. His blood pressure was 124 mm. of mercury systolic and 76 mm. diastolic. His temperature was normal, and his pulse rate was 44 each minute. His voice sounded as though he had an acute cold. Heart tones were somewhat distant, but of good quality. The cardiac rhythm was regular and there were no murmurs. There was a draining sinus in the median line, 1.5 cm. posterior to the anus. The remaining portion of the physical examination gave essentially negative results. His blood count was well within normal limits, and urinalysis and flocculation tests for syphilis

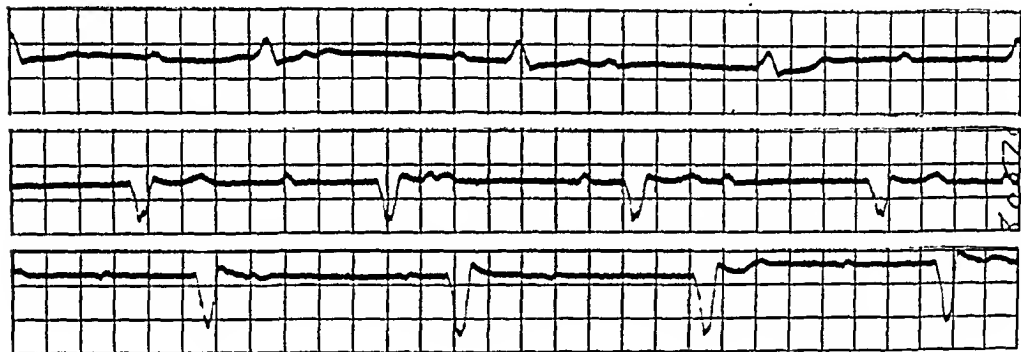


Fig. 1.—Complete A-V dissociation: auricular rate 69 each minute; ventricular rate 41.

gave negative results. Roentgenological studies of his heart did not reveal enlargement. The electrocardiogram revealed a ventricular rate of 41 each minute and an auricular rate of 69, with complete auriculoventricular dissociation. Aberrant QRS complexes and marked left ventricular preponderance were evident.

COMMENT

The long duration of the history of complete heart-block in this case is extraordinary. From the history it is impossible to be certain what acute infection the patient had when he was thirteen years of age. It may have been diphtheria or septic sore throat; either or both could have produced heart-block. I believe there is very little doubt that heart-block had been present constantly since the onset, even through the short period following tonsillectomy when he noticed that his cardiac rate was slightly faster than it usually was; he was not sure what the rate was during this short period.

His cardiac efficiency was about as good when I examined him as it had been since his illness thirty years before. If he restricted his activities somewhat, he had practically no difficulty.

It is to be presumed that the lesion responsible for the block was some acute inflammatory process which by cicatrization brought about the permanent interruption of the functions of the auriculoventricular bundle.

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Department of Reviews and Abstracts

Selected Abstracts

Paul, John R., and Leddy, P. A.: The Social Incidence of Rheumatic Heart Disease. A Statistical Study in Yale University Students. *Am. J. M. Sc.* 184: 597, 1932.

The incidence of rheumatic heart disease in a group of 7914 undergraduate students of Yale University has been found to be 8.2 per thousand as compared with 15 per thousand which is an average figure obtained from statistics of comparable age groups of individuals in other walks of life. Among the men in this group who had attended expensive boarding schools, the incidence was 5.8 per thousand as compared with 12.5 per thousand among those in high schools.

The contention that rheumatic fever is a disease which finds a lower incidence among people of ample means finds support in these observations. According to the methods employed, the factor of poverty does not, however, seem to be as important a predisposing rôle in determining the incidence of rheumatic heart disease as it does in clinical tuberculosis.

Wetherby, Macnider: Chronic Arthritis. A Clinical Analysis of Three Hundred and Fifty Cases. *Arch. Int. Med.* 50: 926, 1932.

Three hundred and fifty consecutive cases of chronic arthritis have been subjected to a clinical analysis. In this series, 68.57 per cent of the patients were women and 31.43 per cent were men. The peak of onset occurred in the fifth decade for both sexes. The duration of symptoms in this series was over one year in 88 per cent and over five years in 55 per cent of the cases.

Monarticular involvement, in a strict sense, was present in only 5 of the 350 cases. A study of the joints involved showed the knees to be affected most frequently in 82.8 per cent of all cases. Other joints commonly involved were the following: fingers, 61.1 per cent; ankles, 58.3 per cent; spine, 57.1 per cent; shoulders, 57.1 per cent; wrists, 50 per cent; hips, 44.6 per cent; and elbows, 42.6 per cent.

There are certain definite sex differences in the distribution of the joints affected, there being a significantly more frequent involvement of the fingers, hands and toes in women and of the spine, hips and feet in men. There is also a marked difference between the sexes in the joints most severely involved, the fingers being the most seriously affected in 16.6 per cent of the women and in only 0.9 per cent of the men, while, on the other hand, the spine was most severely affected in 20 per cent of the men and in only 5.8 per cent of the women.

A study made of the percentage distribution of involvement of the joints by decades showed no striking differences in the distribution in arthritis coming on at different decades of life.

In 32 patients with chronic arthritis there was an acute febrile onset which was similar to the clinical description of rheumatic fever. Such an acute onset was much more frequent in the younger age group. Of this number, 6 (18.7 per cent) had definite rheumatic involvement of the heart. The incidence of rheumatic disease of the heart in the total group of 350 patients was 7 (2 per cent).

Probable sources of streptococcal infection were known to precede the arthritis in 102 cases (29.1 per cent). The more common inciting sources were dental infection, sinusitis, acute respiratory infection, tonsillitis, puerperal sepsis and the puerperium without known infection. Polyarthritides immediately followed definite trauma in 12 cases.

Subcutaneous nodules were sought in 300 consecutive arthritic patients and were found to be present in 94 cases (31.3 per cent). The incidence of subcutaneous nodules was determined for the various age groups; they were found to be present in over 40 per cent of the patients over fifty years of age. Such nodules were found in patients with various clinical and roentgen-ray findings.

Roentgen-ray examinations of all painful joints in 60 consecutive cases have shown a pure type of involvement in only 33.3 per cent, a mixed type in 58.3 per cent and no positive findings in 8.3 per cent of the cases.

Schwartz, Sidney P., and Jezer, Abraham: Transient Ventricular Fibrillation. The Clinical and Electrocardiographic Manifestations of the Syncopal Seizures in a Patient With Auriculoventricular Dissociation. Arch. Int. Med. 50: 450, 1932.

A clinical and electrocardiographic study was made of the syncopal seizures in a patient with auriculoventricular dissociation. More than a hundred electrocardiograms obtained during such seizures revealed the cardiac mechanism to be due to transient ventricular fibrillation.

The natural periods of transient ventricular fibrillation in the patient have varied in duration from only a few seconds to six minutes each, and as many as two hundred and seven attacks of unconsciousness have been observed during a period of twenty-four hours with spontaneous revival. During a period of four months' observation, not a single day passed without the patient experiencing at least one attack.

The premonitory periods preceding a transient seizure of ventricular fibrillation of the ventricles have been variable. They consisted at first of alternate premature beats of the ventricles, which increased the basic ventricular rate. These were followed shortly by irregular periods of recurring groups of aberrant ventricular oscillations, only the first few of which could be heard at the apical region of the heart or felt at the radial pulse.

Pallor of the face and momentary loss of consciousness followed the appearance of these recurrent groups of ventricular oscillations when, during their presence, the pulse disappeared for more than eight seconds but for not more than twelve.

A major attack of unconsciousness with cyanosis, stertorous breathing and convulsions took place when the heart sounds and pulse disappeared for at least twenty but not less than forty seconds. The electrocardiograms made during these periods invariably revealed ventricular fibrillation.

The frequency of the ventricular oscillations during the periods of transient ventricular fibrillation varied from 250 to 500 per minute.

Spontaneous revival from a seizure of ventricular fibrillation was usually ushered in by the appearance in the electrocardiograms of a postundulatory pause, which was followed by an intermediary idioventricular rhythm, as a rule, with an increasingly irregular rate before the restoration of the basic ventricular rhythm.

It is important to appreciate that syncopal seizures in patients with auriculoventricular dissociation are much more commonly associated with transient periods of ventricular fibrillation than has been suspected hitherto.

Rational therapy for the prevention of syncopal seizures in patients with auriculoventricular dissociation depends upon an intimate knowledge of the cardiac mechanism underlying these seizures.

Bedell, Caroline C.: Auricular Flutter With 1:1 Response. Bull. Johns Hopkins Hosp. 52: 225, 1933.

Paroxysmal attacks of 1:1 response occurring during the course of auricular flutter are described in 24 cases. Three of these cases are reported for the first time with electrocardiograms and tabulated analysis of the records obtained. An autopsy report on one of the cases is included. The remaining 21 cases have been gathered from the literature.

One-to-one flutter occurs most frequently in the fifth decade of life. It has not been observed above the age of fifty-seven years, in contrast to other forms of auricular flutter which may occur after the age of seventy years. In other respects the etiology is similar. One-to-one paroxysms occurred during the course of established auricular flutter in which a high grade of block is not established, often with increasing ease and frequency. The attack begins abruptly following exertion. Extreme weakness, shortness of breath and palpitation are the usual manifestations. Syncope, precordial pain and congestive failure may occur. After minutes or hours, the attack subsides gradually. Attacks have followed the administration of quinidine, as well as the combination of atropine and avertin.

The attacks of syncope and possibility of congestive failure during frequent paroxysms somewhat modify the general prognosis in flutter. Digitalis effectively prevents 1:1 paroxysms by increasing the A-V block. During quinidine administration, the patient should be in bed on account of the possibility of paroxysms.

Sigler, Louis H.: Functional Bundle-Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation. Am. J. M. Sc. 185: 211, 1933.

Bundle-branch block complete and partial may be functional in origin caused predominantly by vagal inhibition and fatigue. Restoration of normal QRS complexes in such cases may be accomplished by removal of vagus inhibition where vagal effect is the underlying cause and by local rest where fatigue is the cause.

A paradoxical case is reported where left vagal stimulation apparently removed rather than caused such block. The underlying functional disturbance in this case was apparently fatigue of one of the bundle branches which was sufficiently relieved by increased vagal slowing to permit normal bundle-branch conduction. Abnormal QRS complexes occurred after as long a rest as 0.56 of a second, and normal complexes were restored by additional rest of 0.08 second.

Graybiel, Ashton, and Sprague, Howard B.: Bundle-Branch Block; An Analysis of 395 Cases. Am. J. M. Sc. 185: 395, 1933.

An analysis of 395 cases of bundle-branch block is presented. It is felt that diagnosis of bundle-branch block can only be made with certainty by the use of the electrocardiogram. From the standpoint of diagnosis and prognosis, it is important to determine its presence in cardiac patients.

Bundle-branch block almost invariably indicates serious organic disease of the heart, usually coronary disease; the average duration of life of the 223 fatal cases in this series after the discovery of the conduction fault was one year and two months, but 85 other patients are still alive after an average of two years and eleven months following the discovery of the bundle-branch block. Partial bundle-branch block must be regarded clinically as equally significant with complete bundle-branch block, the prognosis in both being essentially the same.

Conner, Lewis A.: A Discussion of the Rôle of Arterial Thrombosis in the Visceral Diseases of Middle Life, Based Upon Analogies Drawn From Coronary Thrombosis. *Am. J. M. Sc.* 185: 13, 1933.

Attention is called to the fact that whereas thrombosis in the arteries of the heart and of the brain is known to be common and is easy of clinical recognition, almost nothing is known concerning the symptoms of arterial thrombosis in the abdominal viscera. Nevertheless, the frequent occurrence of degenerative changes in the arteries of the pancreas, kidneys, spleen and mesentery indicates that thrombosis in these vessels cannot be rare.

The failure to recognize attacks of arterial thrombosis in the abdominal organs must be due in part to the inherent difficulties of diagnosis, but is almost certainly also due partly to our failure to have the possibility of such attacks in mind and to have accumulated pertinent evidence.

An attempt is made to construct a framework of diagnosis for arterial thrombosis in the kidney, pancreas, spleen and mesentery by utilizing certain symptoms associated with thrombotic infarction in the heart (fever, leucocytosis) and those which result from infarction due to embolism in the kidney, spleen and mesentery.

It seems probable that when both internists and pathologists begin seriously to seek for evidences of such thromboses and to correlate their findings, the difficulties of diagnosis will be found to be not insurmountable and the lineaments of the respective clinical pictures will gradually emerge from the present obscurity, much as have those of the diagnosis of coronary thrombosis.

Coombs, Carey F.: Prognosis in Coronary Thrombosis. *Bristol Med. Chir. J.* 49: 277, 1932.

A sad interest attaches to this paper, the proofs of which were returned by Dr. Coombs on the day before his death from coronary thrombosis. In the same journal are printed a photograph and obituary of Dr. Coombs.

The remarks contained in the paper are based on notes from 144 patients seen by the author. Of the 144 patients, one out of three died in, or shortly after, the attack. He states that the prognosis depends more upon the severity of the attack than upon the background of the patient. He believes that data derived from the state of the peripheral circulation on examination give important information. The immediate danger in cardiac infarction is that the heart will not be able to fill the peripheral circulation. It is this that makes extreme pallor so ominous a symptom. Measurement of the blood pressure also nearly always gives reliable evidence of the extent to which the efficiency of the peripheral circulation is impaired. The most significant feature is the fall in the systolic tension. Also a most direct measure of the efficiency with which the damaged heart is filling the vessels is the pulse pressure. While a low pulse pressure, especially below 25 per cent, is a bad sign, it is not possible to claim that patients with a wide pulse pressure are sure to recover. The author states that if he were compelled to rely for prognosis on one sign alone, it would be the pulse pressure that he would choose.

He points out that with increasing experience it is possible to make a diagnosis of coronary thrombosis in relatively mild cases, and when these are included in a study, the number of patients who recover can be expected to increase.

Symposium on Chronic Myocarditis. New England Heart Association. I. Warren, Shields: The Pathology of Chronic Myocarditis. *New England J. Med.* 208: 573, 1933.

The author discusses only those changes that can be recognized by the pathologist and which are found in certain of the cases of chronic myocarditis. These changes are due principally to impairment of the coronary circulation associated with arterioscle-

rosis or atherosclerosis. He points out, too, the great frequency with which fibrous myocarditis occurs in diabetic autopsies. He believes this is due to the marked degree of arteriosclerosis shown by these cases.

II. Christian, Henry A.: Diagnosis of Chronic Nonvalvular Cardiac Disease (Chronic Myocarditis). New England J. Med. 208: 574, 1933.

Terminology is unsatisfactory. Chronic nonvalvular cardiac disease, if one understands that the pericardium is not concerned, is satisfactorily descriptive. Chronic myocarditis carries the idea of inflammation with connective tissue proliferation and this usually is lacking. However, in classical Greek the termination "itis" did not mean inflammation of but merely "concerning, of or about," and in this classical sense chronic myocarditis is a justified title.

Chronic myocarditis constitutes half of cardiac patients in an adult clinic: incidence increased with advancing years; rare before 45 except after hypertension; may occur at any age from the cradle to the grave.

Symptoms are those of cardiac insufficiency of any cause.

Physical examination shows cardiac enlargement; in obese or emphysematous patients x-ray pictures may be needed to determine the size of the heart. Very rarely the heart is not enlarged.

A murmur, systolic in time, often is present, but there may be no murmur; if present, may be of any intensity or distribution; basal diastolic murmur sometimes is heard, due to dilatation of aortic or pulmonic orifice.

Rhythm is regular or irregular; extrasystoles are most frequent; auricular fibrillation is next in frequency; bundle-branch block or intraventricular block is quite often shown in electrocardiogram; bundle-branch block is often detectable by inspection and palpation as pointed out by John T. King, Jr.

Hypertension is often present and is an important etiological factor, but in some patients is never present. Arteriosclerosis, especially of coronary arteries, has the same relation; syphilis is not an etiological factor except exceedingly rarely.

In a high percentage of cases, clinical diagnosis is confirmed at autopsy.

III. Jackson, Henry: Treatment of Nonvalvular Heart Disease of Middle and Old Age. New England J. Med. 208: 574, 1933.

The author discusses the various measures which are recognized to be of value in preserving such patients from further strain on their heart. He also discusses briefly the use of digitalis, nitroglycerine and similar drugs.

Brown, Madelaine R.: A Study of the Pathogenesis of Myocardial Fibrosis ("Chronic Fibrous Myocarditis"). Am. J. M. Sc. 184: 707, 1932.

The material for this study consists of 1000 consecutive autopsies of which 110 described areas of scar tissue in the myocardium. It was not evident from a study of these cases that infectious diseases or toxins gave rise directly to fibrosis of the myocardium, although they may be concerned in producing arteriosclerosis of the coronary arteries. Direct invasion of the heart muscle in syphilis and rheumatism plays a minor rôle in the pathogenesis of myocardial scarring.

Disease of the coronary arteries which was present in 70 of the 110 cases causing either infarction or more slowly produced ischemic necrosis of the muscle fibers, is advanced as the important etiological agent of myocardial scarring ("chronic fibrous myocarditis").

Lisa, James R., and Ring, Alfred: Myocardial Infarction or Gross Fibrosis. Analysis of One Hundred Necropsies. Arch. Int. Med. 50: 131, 1932.

A series of 100 autopsies showing myocardial infarction or gross myocardial fibrosis, consisting of 10.6 per cent of 942 autopsies performed is analyzed. Thirty-two of these cases showed definite recent cardiac infarction, while 68 showed fibrotic patches interpreted as probable old infarction. Eighty-three were in males, 17 in females. The average age of all patients was 60.8 years. The youngest was twenty-eight years old, the oldest eighty-three years. The average weight of the heart was 519 gm. Most of the lesions were located in the left ventricular wall or involved the left ventricle and interventricular septum, but in 14 cases the lesions were confined to the septum alone. Approximately 83 per cent showed moderate to marked coronary sclerosis. Coronary thrombosis was noted in 24 cases; in 3 there was thrombosis of both the left and the right coronary artery. Mural thrombosis occurred in 34 cases, in 16 of which there had been recent infarction. Aneurysm of the left ventricle was noted in 5 cases; chronic adhesive pericarditis occurred in 10. Ten patients had positive Wassermann reactions, while 9 others showed evidence of vascular syphilis at autopsy. Hypertension occurred in approximately 60 per cent of the cases. In 24 cases in which electrocardiograms were taken, the most frequent change was abnormality of the T-wave, which occurred in 23. Seventeen cases showed abnormalities of the QRS complex, 5 auricular fibrillation and 1 complete heart block. Fifty-six cases presented cardiac symptomatology, while in the remaining 44 the symptoms were referred to some other organ. Eight of the 12 sudden deaths in the series were due to recent cardiac infarction.

Bach, Francis, and Bourne, Geoffrey: Permanent Organic Cardiovascular Disease After Thyrotoxicemia. Quarterly J. Med. 1: 579, 1932.

The authors have studied 36 patients who had previously suffered from active thyrotoxicosis in whom no signs of present thyroidal activity were discoverable when re-examined for cardiovascular abnormality.

It is concluded from this study that thyrotoxicosis does not produce permanent changes in the normal heart. It may produce an additional myocardial change in hearts affected by some other cause of myocarditis, or predisposed to arteriosclerosis. The disease may initiate hypertension presumably in individuals predisposed to that condition.

Book Reviews

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM, INCLUDING THE CARDIAC ARRHYTHMIAS. By Harold E. B. Pardee, M.D. Pp. 295, with 74 illustrations. New York, Paul B. Hoeber, Inc., 1933, third edition.

The fact that this excellent manual has now required a third edition is eloquent testimony both to the merit of the book as a clinical guide and to the rapid growth of the science of clinical electrocardiography. The latter has made necessary extensive rewriting of many of the chapters and the addition of much new material. It is interesting to note that in the discussion of the localization of ventricular premature beats and of the myocardial lesions giving rise to bundle-branch block, the more recent views as to localization are accepted by the author.

This new edition fully merits a continuance of the popularity earned by the earlier ones.

INFARTO CARDIACO. By Pedro A. Castillo, M.D., Profesor de Clinica Medica, Havana. Pp. 351, with 99 figures, 2 colored plates. Havana, Talleres Tipograficos "La Propagandista," 1931.

Professor Castillo's book on cardiac infarction should be of interest and value to Spanish-speaking physicians. No new facts or startling theories are expressed, but the different aspects of coronary thrombosis are discussed from the author's experience and from his wide knowledge of the literature, and reports of 29 cases—some with post-mortem observations—are included. The material is arranged in orderly sequence; the volume is generously illustrated; and there is a long bibliography. Evidences of hasty proof reading mar an otherwise excellent book.

E. H.

NOUVEAU TRAITE DE MEDICINE. FASCICULE X. PATHOLOGIE DE L'APPAREIL CIRCULATOIRE (COEUR ET VAISSEAUX). Vol. III, pp. 720. Masson & Cie. Paris, 1933.

This volume—the work of Drs. Bickel, Courcoux, Dumas, Durand, Gaugier, Goyet, Gravier, Legry and Lelong—deals with diseases of the blood vessels and completes the series of three volumes on the pathology of the circulatory system. More than half the pages are devoted to aortitis, aneurysm, arteritis and arterial tension, with shorter sections on thrombo-angiitis obliterans, periarteritis nodosa, arterial embolism and diseases of the veins. The work is carefully prepared and well illustrated and in general plan is similar to the earlier volumes.

E. H.

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Original Communications

PRODUCTION OF THE ANGINAL SYNDROME BY INDUCED GENERAL ANOXEMIA*†

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IN INDIVIDUALS subject to attacks of chest pain in whom there are neither physical signs nor electrocardiographic evidence of an appropriate cause, it is often impossible to ascertain the origin of the pain. Chest pain in the individual with a normal heart may be mistakenly diagnosed as angina pectoris. On the other hand the patient with angina pectoris may be assured of a normal heart yet die within a short time of coronary occlusion. The clinical recognition of impaired coronary circulation is therefore difficult as well as important.

Several clinical peculiarities of angina pectoris have drawn our attention and indicate that the pain arises from a localized, sensitive area of myocardium affected by any of a number of stimuli. For example:

1. The pain in some cases appears only at the beginning of effort—the patient is unable to “shift gears” quickly. If the patient makes the same effort but starts gradually he does not develop pain. In explanation, we assume that sudden nutritional demands by the myocardium initiate the pain.

2. Many patients develop pain on exposure to cold. External cold, in this instance, acts as a stimulus.

3. The site of coronary occlusion is localized. The majority of coronary thromboses occur in one area, namely, in that supplied by the anterior descending branch of the left coronary artery.

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†A preliminary report of the results described in this communication was read before the Society for Experimental Biology and Medicine (Rothschild, M. A., and Kissin, M. Proc. Soc. Exper. Biol. & Med. 29: 577, 1932).

‡Aided by a grant from the Herbert L. Celler Foundation.

4. Many patients with angina pectoris are free from pain or have less pain following recovery from an attack of coronary occlusion.¹ This occurs because the localized, sensitive area previously supplied by the occluded artery has been replaced by fibrous tissue (infarction) and is no longer capable of conducting painful sensations.²

The theory that angina pectoris is due to stretching of a diseased aorta is losing ground. The opinion prevails today that myocardial ischemia is the cause of the pain.² Keefer and Resnik³ have gone a step further and on theoretical grounds have concluded that myocardial anoxemia is the cause of anginal pain.

These considerations led us to investigate the effect of gradually induced general anoxemia on two groups of individuals, one having impaired coronary circulation, the other having unimpaired coronary circulation. We felt that cardiac anoxemia (which is part of general anoxemia) might be a means of inducing precordial pain and that the response to anoxemia might serve to distinguish between chest pain due to impaired coronary circulation and chest pain arising from other causes.

THE SUBJECTS

Anoxemia was induced in 46 individuals, several of whom were subjected to the experiment twice. The cases were divided into two groups:

A. Control cases.

B. Cases of angina pectoris.

The control group consisted of three sub-groups:

1. Normal individuals with no history of precordial pain, no cardiac symptoms, and no objective signs of cardiac disease. (Normal controls.)

2. Individuals without precordial pain but with subjective complaints related to the circulatory system and with objective evidence of cardiac disease such as valvular defects or hypertension. (Cardiac controls.)

3. Individuals having a history of pain in the left chest not due to impaired coronary circulation; the diagnoses were spondylitis, brachial neuritis, rheumatic carditis, cholecystitis, etc., but not angina pectoris. (Pain controls.)

The cases of angina pectoris consisted of two sub-groups:

1. Individuals with a history of precordial pain and with objective evidence of myocardial disease such as enlarged heart, hypertension, harsh systolic murmurs (due to sclerosis of the heart valves or roughening of the aorta), dilatation or sclerosis of the aorta (determined by roentgenological examination), and electrocardiographic changes suggestive of impaired coronary circulation. (Angina with objective findings.)

2. Individuals with a history of precordial pain but with slight or no objective evidence of myocardial disease. The diagnosis here rested on the evaluation of symptoms. (Angina without objective findings.)

The cases were divided numerically as follows:

Control group 1 (normal)	-----	4 cases
Control group 2 (cardiac)	-----	5 "
Control group 3 (with pain)	-----	11 "
Angina group 1 (with objective findings)	-----	18 "
Angina group 2 (without objective findings)	-----	8 "

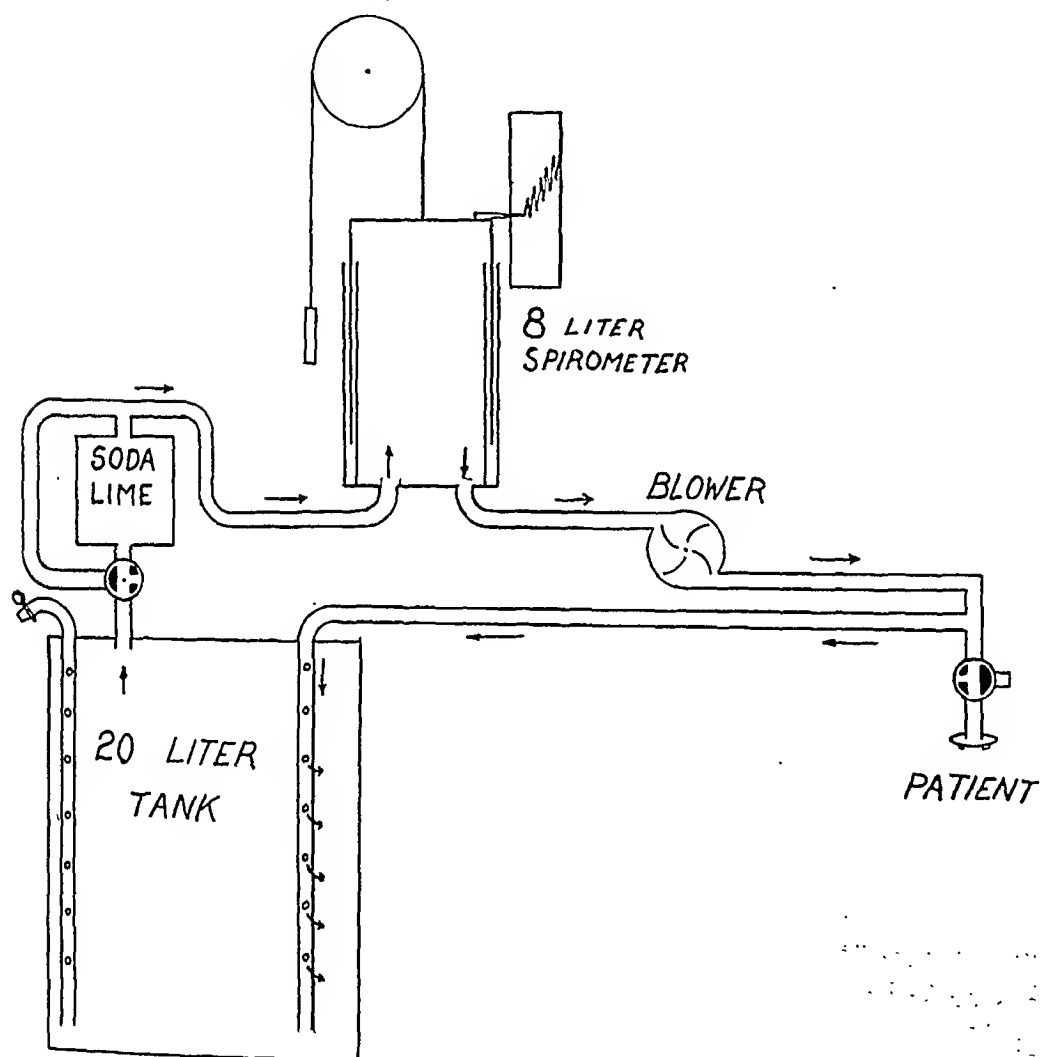


Fig. 1.

METHOD

Anoxemia was induced by rebreathing. The rebreathing apparatus (Fig. 1) was improvised from a basal metabolism spirometer of 8 liters capacity to which was attached in series a 20 liter tank. The rebreathing system contained, therefore, 28 liters in all. A motor blower maintained the circulation. Attached to the top of the larger tank was a

cylinder containing soda lime. At the base of the cylinder was a valve which could be turned to permit the soda lime to be either in or out of the rebreathing system. In this way we could control the absorption of carbon dioxide, either removing it or permitting it to accumulate. A graphic record of the respirations was taken.

Before anoxemia was induced the spirometer was filled with oxygen, and the patient rebreathed an oxygen rich mixture for ten minutes. During this control period the patient was made familiar with the apparatus, was permitted to relax, and was reassured of the harmlessness of the test.

The apparatus was then filled with room or outside air, and electrocardiographic leads were applied to the patient. The confidence of the patient having been won during the control period, he was given an explanation of the procedure to follow. He was told that during the second breathing test he would be uncomfortable, that he might become dizzy, or develop headache, or suffer palpitation, that none of these discomforts would be severe, and that they would disappear as soon as the test was stopped. He was told that these uncomfortable sensations should cause no alarm, that they were an evil necessary for the successful performance of the test. It was explained that certain changes appeared in the electrocardiogram during the breathing test that were not otherwise present and that it was necessary for him to withstand the discomforts so that we might obtain more information about his heart. We further told him that we did not wish him to become too uncomfortable, that when he felt he could no longer tolerate the discomfort he was to raise his hand as a signal to stop. We asked, however, that he continue for as long a time as he could because the longer he breathed through the apparatus, the more information we could obtain.

No mention was made of the chest pain that might develop because we did not wish to influence the patient by suggestion. Furthermore, in order to obtain unbiased results, the operator himself knew nothing of the clinical status of the patient prior to the performance of the experiment.

Questions were asked of the patient after the experiment. Suggestion was carefully avoided as before. He was asked if he had experienced dizziness, headache, or palpitation. Whenever pain had been felt, this was, with few exceptions, volunteered spontaneously. The patient was asked his reasons for not wishing to continue rebreathing. The usual reason was pain or respiratory difficulty. But some of the answers were, to say the least, disturbing.

We were told, for instance, "I was afraid I was going to get an attack of pain," or "My doctor told me that I am not sensitive and I don't know when I feel pain, so I was afraid I was injuring myself

without knowing it," or "You told me it would take ten minutes and I saw that the time was up," or "I saw that the lines on the breathing chart were running together." Such experiments were, of course, discarded.

The disadvantage of the rebreather employed was the inability of the patient to talk during the experiment. Since the breathing tube was in the mouth, the subject had to wait to make comments or complaints until the termination of the test. Ideally, we should like to have had a cabinet or transparent head covering in which the patient might be observed and blood pressures, electrocardiograms, and blood samples taken, yet in which the patient could speak.

For a brief time, we used instead of a rebreathing system, a mask through which a 6 per cent oxygen mixture was administered to the patient. This proved unsatisfactory because anoxemia developed too rapidly. Instead of developing precordial pain, the patient lost consciousness. This sometimes occurred with the rebreathing method of inducing anoxemia. Schneider⁴ has shown that when anoxemia is induced rapidly, the symptoms appearing are cerebral, but when anoxemia is induced more slowly the circulatory system responds. Therefore, with our technic we endeavored to establish the period of rebreathing as from 10 to 15 minutes. Actually, the period varied from 8 to 23.5 minutes, except in two cases of 4 and 6 minutes, respectively. The disadvantages of continuing too long were the discomforts of dryness of the throat, pinching of the nose by the nose clamp, pressure of the electrodes or bandages, or lying in one position for too long a time.

At the end of each rebreathing period a specimen of air was taken from the auxiliary tank and examined with the Haldane apparatus for its oxygen and carbon dioxide content.

The oxygen content of the inspired air furnished a good index of the degree of anoxemia. When the oxygen level reached 12 per cent, there were rarely symptoms of oxygen lack. At 11 per cent, anoxic symptoms occasionally appeared. At 10 per cent, symptoms were almost always present, and at 8 per cent they were always present. Furthermore, by watching the ear for cyanosis, we were able to estimate the degree of anoxemia. At 12 per cent, there was rarely cyanosis; at 11 per cent there was occasionally slight cyanosis; at 10 per cent moderate cyanosis was the rule, and at 8 per cent or less there was marked cyanosis.⁵

Nevertheless, the oxygen level of the blood does not follow exactly the oxygen level of the inspired air. Loewy⁶ showed that the oxygen tension in the alveoli sinks to between 30 and 35 mm. of mercury before signs of oxygen lack appear. The percentage of oxygen in the inspired air which gives an alveolar oxygen tension of 30 to 35 mm. varies with the depth of respiration. With shallow respirations, the

inspired air may contain as much as 12 per cent oxygen, while the alveolar tension is 35 mm. With deeper respirations, 9 to 10 per cent oxygen in the air will give an alveolar tension of 35 mm. It is therefore more difficult to render a subject anoxemic if he breathes deeply.

Blood gas studies were not made. In order to study the arterial oxygen, it would have been necessary to puncture an artery. This is frequently painful and adds a psychic factor. Often, too, a minute or more is required before one can obtain the blood sample. Once the patient has signalled for the test to be stopped, a minute is too long a time to continue. Every second is important lest the patient lose consciousness or detach the mouthpiece. Arterial blood determinations were, therefore, not feasible. However, blood gas studies are in order. It remains to devise a technic for collecting blood specimens without interfering with the experiment.

RESULTS

The effect of induced anoxemia in our subjects was as follows:

Control Group	1 (normal),	4 subjects, 0 developed pain
	2 (cardiac),	5 subjects, 0 developed pain
	3 (pain),	11 subjects, 0 developed pain
Angina Group	1 (objective findings),	18 subjects, 11 developed pain
	2 (no objective findings),	8 subjects, 7 developed pain

Of 26 individuals suffering from angina pectoris (impairment of the coronary circulation), 18 developed precordial pain during induced general anoxemia and 8 did not. Twenty control subjects did not experience pain.

Pain appeared when the oxygen level fell to between 11 and 6 per cent. The pain was identical in character and distribution with the pain of which the patient gave a history except that it was generally milder. Occasionally, however, the attack of pain produced was more severe than the spontaneous attacks. A patient who gave a history of pain beginning in the left elbow radiating to the chest, developed a pain in the same site and with the same radiation during anoxemia. Several patients remarked, "This is the same pain that bothers me." The pain subsided, as a rule, as soon as air (20.9 per cent oxygen) was admitted to the lungs. Occasionally, the pain persisted for several minutes after the end of the experiment. On three occasions it was necessary to administer amyl nitrite for relief of the pain.

In order to rule out the possibility that the increased respiratory activity which appears during anoxemia is the cause of the anginal attacks, we investigated the effect of hyperventilation without anoxemia on thirteen individuals who had developed pain during anoxemia. Carbon dioxide inhalations were used to reproduce the deep breathing appearing in the last few minutes of the anoxemic period.

The rebreathing apparatus was filled with oxygen (25 to 40 per cent), and the patient was connected to it. For the first five to seven minutes the carbon dioxide was absorbed, then the valve was turned so that the carbon dioxide accumulated. Almost immediately thereafter an increase in the rate and depth of respiration began and continued progressively until the end of a ten-minute period. The carbon dioxide content of the inspired air at the end of the experiment varied from 1.2 to 3.7 per cent (average 2.1 per cent). Pain appeared in but one case (q.v.) and was caused, without doubt, by the excitement of the experiment.

Several experiments illustrate significant points and are therefore considered individually.

One patient (M. W.) developed an attack of pain during the control period as well as during the anoxemic period of rebreathing. During the anoxemic period he did not become cyanotic (the oxygen level of inspired air at the end of the experiment was 12 per cent); although the attack of pain which developed was much more severe than the attack he experienced during the control period. We attributed both attacks to the excitement of the experiment and did not include him in the series. Clinically, the patient had frequent and severe attacks precipitated by slight excitement.

One patient (Case 34) did not develop pain when he reached an oxygen level of 12.9 per cent. When later the test was repeated and he reached 8.8 per cent, he developed pain. Another patient (Case 36) developed no pain at 7.4 per cent. When the experiment was repeated at a later date, she developed an attack at 9.6 per cent. She gave a history of pain brought on by exertion or excitement on each occasion, but for the month before the second test her condition had been worse. These two cases illustrate that factors in addition to anoxemia, per se, are in part responsible for the production of pain.

One patient (Case 10), a man of forty-three years, with rheumatic heart disease, mitral stenosis, aortic insufficiency, and auricular fibrillation, came into the hospital with acute, severe precordial pain unrelieved by nitroglycerin and $\frac{3}{4}$ grain of morphine sulphate. The diagnosis of coronary occlusion was made and he was treated accordingly. Several weeks later, the anoxemia experiment resulted negatively for pain, the oxygen level reaching 6.1 per cent. A month later he died, quite suddenly, from cerebral embolus. Post-mortem examination revealed healthy coronary arteries. There was both an old and recent rheumatic infection of the heart.

One patient (Case 38) in whom we were able to precipitate an attack of pain, was classed originally in the group without objective evidence of myocardial damage (angina group 2). Later, electrocardiographic evidence of myocardial damage became overt, the T-wave became flat in Lead I and inverted in Leads II and III, and we changed

the classification to angina group 1, i.e., with evidence of impaired coronary circulation. This indicates the potential value of the anoxemia test in establishing the diagnosis of coronary artery disease while there are only subjective symptoms.

In Case 27, the subject was classed in the series that did not develop pain. However, he did develop a "heaviness of the chest" during anoxemia. The patient gave a history of attacks of "heaviness of the chest" associated with precordial pain. Inasmuch as we were unable to reproduce the attack in its entirety, we omitted this case from the list of those in whom we were able to precipitate an anginal attack.

The experiments were begun two years ago. During the course of developing the technic, more than one hundred tests were made. The patients have been closely followed, and there have been no untoward effects as a result of the experiments.

DISCUSSION

In cases with definite impairment of the coronary circulation we hesitated to continue the experiment beyond the point of evident discomfort. We believe that more individuals would have developed pain had anoxemia been continued. By reference to Table I showing the oxygen levels reached by our cases of angina pectoris, it will be seen that five subjects who did not develop pain did not go below 8 per cent. On the other hand, in the cases that developed pain, it will be noted that pain did not appear at times until the oxygen level reached 7 per cent. In one instance, with a very cooperative and calm patient, pain appeared only at 5.9 per cent. Furthermore, as time went on and our technic improved, the percentage of patients with clinical coronary artery disease in whom we were able to reproduce pain increased. In the first 21 experiments on subjects with angina pectoris, 12 subjects experienced pain, whereas in the last 7 experiments on the same group, 6 subjects experienced pain. In addition, two subjects who did not develop pain at the first trial, at the beginning of our experiments, did later at a second trial.

It is a well-known clinical fact that after cardiac infarction patients frequently have less severe pain than in the prethrombotic stage. This may explain why the definitely anginal group showed such a high per cent that did not develop pain. The stimulus, anoxemia, was inadequate and we were unable to pass the pain threshold.

Further analysis of Table I reveals no relationship between the oxygen level and the onset of pain. We are unable at present to demonstrate an oxygen level at which pain commences or ceases. More important is the relation between the sensitiveness of the patient and the degree of anoxemia necessary to initiate pain. In several instances Libman's pain test⁷ was made (unfortunately not in all cases), and it

was found that at least two of the subjects in whom we were unable to produce pain were hyposensitive. A large series of individuals must be studied, however, before final conclusions may be drawn.

TABLE I
OXYGEN LEVEL AT END OF EXPERIMENT IN ANGINOUS CASES

	CASES DEVELOP- ING PAIN	CASES NOT DEVELOP- ING PAIN
Group I (with objective evidence of myocardial disease)	6.4%	6.4%
	7.1	*7.4
	8.4	7.9
	8.6	7.9
	8.6	8.0
	†8.8	8.1
	9.4	9.4
	*9.6	9.8
	9.9	†12.9
	11.2	
	11.2	
Group II (without objective evidence of myocardial disease)	5.9	8.7
	8.4	
	8.8	
	8.9	
	9.1	
	9.6	
	9.8	
Average for Groups I and II	8.8	8.5

†, * Same case.

TABLE II
PERCENTAGE OF OXYGEN IN INSPIRED AIR AT END OF EXPERIMENT

CONTROL GROUP I	CONTROL GROUP II	CONTROL GROUP III	ANGINA GROUP I	ANGINA GROUP II
6.1	6.4	6.4	6.4	5.9
7.8	7.8	6.8	6.4	8.4
8.1	8.1	7.0	7.1	8.7
8.9	8.3	7.5	7.4*	8.8
	8.7	7.7	7.9	8.9
		8.1	7.9	9.1
		8.5	8.0	9.6
		8.8	8.1	0.8
		8.8	8.4	
		9.6	8.6	
		10.3	8.6	
			8.8†	
			9.4	
			9.4	
			9.6*	
			9.8	
			9.9	
			11.2	
			11.2	
			12.9†	
Average 7.7	Average 7.9	Average 8.1	Average 8.85	Average 8.6
Average for all control cases 8.0			Average for all anginous cases 8.8	

*, † Same case.

Examination of Table II showing the percentage of oxygen in the inspired air at the end of each experiment, demonstrates no appreciable difference between the oxygen level reached by the controls and by those with impaired coronary circulation. This supports the view that the response to anoxemia is not a test of cardiac function.⁸

One may ask why our control subjects did not experience pain. If myocardial anoxemia is a cause of anginal pain, then any myocardium, damaged or sound, when anoxic, should be painful. There are several answers to this question. First, the degree of anoxemia in our control subjects, although the same as in our cases of angina pectoris (Table II), may have been insufficient to produce pain. It may be that the heart with a good blood supply requires a greater degree of oxygen deprivation for the initiation of pain than the heart with impaired circulation. Second, it is possible that the hearts of our control subjects were hyposensitive, that there existed no areas of increased sensitivity as in individuals suffering from angina pectoris.* Hence, our stimulus, cardiac anoxemia, could not excite pain. Third, there occurred in our control subjects, during general anoxemia, a compensatory dilatation of the coronary arteries (Hilton and Eicholtz,⁹ Gremels and Starling,¹⁰ Hammouda and Kinoshita,¹¹ whereby an adequate oxygen supply to the myocardium was maintained. On the other hand, in our subjects who suffered from angina pectoris, the coronary arteries were sclerotic and rigid and unable to dilate during anoxemia. Hence the myocardium became anoxic and the patient felt pain.

Table III illustrates that during the control period of hyperventilation without anoxemia, the minute volume of the respiration tended to increase during the last five minutes, and that during the anoxic period the same increase usually but not always appeared. In other words, the minute volume of the respiration was increased, as a rule, under both conditions. We feel, therefore, that respiratory effort played little or no rôle in the causation of pain.

In addition to lack of oxygen, other factors may affect the heart during anoxemia. During anoxemia, tachycardia develops, the diastolic blood pressure falls,^{12, 13} the pulse pressure rises,^{12, 13} and the minute volume output of the heart increases.¹⁴⁻¹⁹ One may therefore protest that unless these factors are controlled, it is not possible to hold anoxemia, per se, responsible for the pain. One may insist that the decreased efficiency of the heart during tachycardia, the inability of the heart to make the best use of its nutritive supply, is the cause of the pain. Or one may attribute the pain to the diminished coronary blood flow that accompanies a fall in diastolic blood pressure.²⁰ The rise in pulse pressure may be held accountable, since a heart works harder

*This lack of cardiac sensitivity may explain why those of our control subjects who had essential hypertension and probably some degree of coronary sclerosis had no pain clinically or experimentally.

TABLE III
VOLUME OF THE RESPIRATION IN LITERS PER MINUTE DURING REBREATHING

CASE	PE- RIOD	MINUTE																								
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
30	C*	10.5	11.1	10.5	11.4	10.5	10.6	10.9	10.2	11.2	12.5															
	A*	11.1	11.3	10.9	11.5	11.8	10.7	11.5	11.5	12.0	12.5	15.6	16.6	16.9												
33	C	6.5	6.9	7.1	7.5	8.3	8.2	9.1	9.0	9.5	9.2	10.3	10.2	11.1	10.7	11.1	11.2									
	A	7.3	8.9	9.5	9.1	9.9	10.3	11.0	12.0	12.2																
34	C	9.7	8.3	9.4	9.0	8.7	10.0	9.3	10.1	10.9	12.6															
	A	10.1	10.7	10.0	11.5	11.3	11.9	12.9	14.7	14.8																
36	C	5.0	4.8	5.0	5.1	5.6	5.8	6.0	5.8	6.2	7.7															
	A	4.5	5.5	5.2	5.7	6.8	6.2	6.6	6.5	7.2	6.3															
39	C	9.5	9.5	9.3	9.3	9.2	9.0	9.6	10.6	11.2	12.7															
	A	10.2	10.3	10.4	10.0	10.0	10.6	10.5	9.8	10.4	10.2	9.8	9.6	10.0	10.4	10.9	9.8	10.2	9.7							
40	C	10.8	10.8	10.6	9.9	9.4	8.1	9.5	9.4	9.3	8.4															
	A	8.7	10.0	10.2	8.9	8.6	8.0	7.5	8.2	8.1	8.1	8.5	8.9	8.8	9.2	9.4	9.6	9.9	10.4	10.8	12.3	12.5	17.4	18.6		
41	C	6.0	6.4	7.4	8.2	8.8	8.7	8.6	8.1	9.5	9.8															
	A	8.1	9.6	7.9	6.7	6.9	7.1	7.3	7.4	7.7	7.6	8.2	7.8	7.8	8.0	9.2	9.5	9.4	10.0	10.0						
42	C	7.4	10.3	8.4	9.2	10.6	9.9	8.5	9.8	7.0	7.0															
	A	8.0	7.5	7.5	7.6	8.0	6.8	8.1	7.2	7.4	7.2	7.5	8.2	7.8	9.0	8.3	9.8	10.0								
43	C	7.0	7.5	6.7	7.7	8.8	9.3	8.1	8.0	8.8	8.2															
	A	7.0	7.4	8.1	8.2	10.1	8.9	10.8	10.1	10.4	10.9	9.7	9.4													
44	C	9.5	7.2	7.6	9.6	7.2	8.0	8.5	7.3	7.6	8.7															
	A	7.6	7.4	6.2	5.6	4.9	5.6	4.9	5.6	4.3	6.8	6.2	6.0	5.7	6.0	6.1	5.9	7.0	4.8	6.6	7.4	5.0	6.7	6.0	6.7	
45	C	9.0	9.0	10.0	10.0	9.8	9.5	9.6	10.8	11.8	11.8															
	A	9.4	9.7	9.2	9.3	9.3	9.4	10.0	10.0	10.4	11.0	11.8	12.1	13.1												
47	C	17.3	11.7	14.3	11.3	10.5	10.3	10.7	11.3			11.8	12.1	13.1												
	A	10.5	13.3	12.8	16.6	12.4	12.0	10.1	11.0	10.6	9.6	8.2	7.9	6.6	6.2	6.7	8.2									

* C, means control; A, means anoxemia.

when the pulse pressure rises. Finally, the increased work of the heart from a rise in the minute volume output during anoxemia may be held responsible for the pain.

But leaving these considerations aside, we have confirmatory evidence that anoxemia is the cause of the pain, from a recent study²¹ by one of us on the effect of anoxemia on exercising skeletal muscle. It was found that oxygen lack is an important contributing cause of the pain experienced in an exercised muscle.

SUMMARY

1. Anoxemia was induced by rebreathing in 26 subjects with angina pectoris (impaired coronary circulation). Eighteen of the 26 experienced an attack of precordial pain. Twenty control subjects did not develop pain.

2. The induced attacks were identical in character with the spontaneous attacks.

3. Anoxemia is in part responsible for the pain of angina pectoris.

4. The response to induced anoxemia is of value in the diagnosis of impaired coronary circulation. Only persons with angina pectoris experienced pain during anoxemia.

After our preliminary note had been issued and after this manuscript had been composed, a report appeared by Dietrich and Schwiegk (Dietrich, S., and Schwiegk, H.: *Das Schmerzproblem der Angina Pectoris*, Klin. Wchnschr. 12: 135, 1933) confirming our results.

The following are representative protocols:

Case 8, control group II, male, forty-two years old. Three months before the patient began to notice swelling of the ankles which subsided almost completely with rest in bed. Otherwise, he felt well. Physical examination, including the heart and eye grounds, was negative. Urinalysis revealed casts, albumin, and red blood cells; specific gravity 1.010 to 1.022. Basal metabolism: -28, -20, -8, -25. Blood pressure: 110/60. Roentgenogram of the chest showed moderate generalized enlargement of the cardiac shadow and moderate dilatation of the aorta. Electrocardiogram: negative. Diagnosis: *Nephrotic stage of chronic glomerular nephritis*. Anoxemia: The experiment lasted 13.5 minutes. The oxygen content reached 8.3 per cent, the carbon dioxide 0.2 per cent. The heart rate increased from 80 to 130. The experiment was stopped because of difficulty in breathing. There was no precordial pain. The electrocardiogram showed flattening of the T-waves in Leads I and II. The T-wave of Lead III became less inverted. The S-T segment of all three leads showed a drop of about 1 mm. in the last minute.

Case 17, control group III, male, thirty-six years. The patient complained of pains across the chest and down both arms coming in attacks for the past two years. The first attack came while the patient had been playing polo after he had been hit on the left side of his chest with a polo ball. The pain then radiated across the chest and down both arms. There was shortness of breath associated with it. The attack lasted about three hours. He had six attacks since then, the last one a week before while sitting at the desk. The patient felt "as if somebody were tearing

out his lungs." There was no sense of pressure. Prostration did not follow the attacks. He was able to go about and do anything during the pain. The patient climbed two flights of stairs six to seven times a day without discomfort. He complained also of a pain in the neck, more on the right side, radiating to the shoulder blade, not related to change in the weather and not relieved by nitroglycerin. Physical examination revealed diseased tonsils from which pus could be expressed. The heart sounds were normal. The right trapezius muscle was tender and spastic. There was tenderness along the right side of the cervical vertebrae. The lungs showed no abnormalities. Blood pressure: 110/90. Fluoroscopy showed the heart to be normal. Electrocardiogram: low voltage. Diagnosis: *Spondylitis of traumatic origin*. Anoxemia: The experiment lasted fourteen minutes, the oxygen level reached 7.0 per cent, the carbon dioxide 0.06 per cent. The heart rate increased from 88 to 105. The experiment was stopped because of difficulty in breathing. Precordial pain did not develop. In the electrocardiogram, there developed flattening of the T-wave in Leads II and III.

Case 18, control group III, male, forty-two years old. At the age of eighteen years the patient suffered an attack of rheumatic fever which required bed rest for three months. The patient had at that time pain in the joints but no fever, nor redness or swelling of the joints. Since that time he had pain in the back. For the past five to six years there had been a steady pain behind the sternum. The pain was no worse on effort. The pain was not present on arising, but as the day went on the pain appeared and became progressively worse. Upon the patient's going to bed, the pain disappeared. There was no shortness of breath on walking. The pain radiated around the left side to the back. Physical examination: The heart was regular and slow, the sounds were of good quality and there were no murmurs. There were no positive findings. Blood pressure: 140/80, 170/110. Roentgenograms showed normal heart and lungs. The esophagus was markedly dilated, and there was spasm of the cordia. Electrocardiogram: negative on two occasions. Diagnosis: *Cardiospasm* (improved with atropinization). Anoxemia: Duration of the experiment twelve minutes, oxygen level reached, 10.3 per cent, carbon dioxide 0.7 per cent. No electrocardiograms were taken. The experiment was halted because of faintness, weakness, and difficulty in breathing. Precordial pain did not develop.

Case 22, Coronary group I, male, fifty-six years old. One and one-half years before the patient had suffered a "heart attack." Since that time he became easily fatigued and short of breath and was compelled to use two pillows for sleep. He had attacks of dull pain in the left side of the chest radiating to the left arm, brought on by exertion. The apex of the heart was in the fifth interspace, 9 cm. to the left of the midline. There was gallop rhythm, and a systolic and diastolic apical murmur. The chest was emphysematous. The liver edge was two fingers below the costal margin. Blood pressure: 140/105. Electrocardiogram: Inverted T-wave in Lead I. Intraventricular block. Diagnosis: *Coronary artery disease*. Anoxemia: The experiment lasted ten minutes. The oxygen reached 9.8 per cent, the carbon dioxide 0.1 per cent. The pulse rate fell from 80 to 70. In the last two minutes, the electrocardiogram showed a drop of 1 mm. in the S-T segment of Lead III. The experiment was stopped because of difficulty in breathing. Palpitation developed, but no precordial pain.

Case 23, Coronary group I, male, fifty-six years old. The patient was diabetic for two years. For six months he suffered mild pain over the heart, squeezing in nature, radiating to the right arm. Eight weeks ago, he suffered a coronary occlusion. He was taken to Beth Israel Hospital where he remained for six weeks. Since discharge from the hospital he felt weak and complained of shortness of breath and mild attacks of pain in the left chest. The pain was less intense than before en-

trance into the hospital. The heart sounds were poor. There were no murmurs. The chest was emphysematous. Blood pressure: 110/78. Electrocardiogram: Low voltage QRS and T in all leads. Diagnosis: *Coronary sclerosis; occlusion with healed infarction*. Anoxemia: The experiment lasted almost twelve minutes. The oxygen level reached 8.1 per cent, the carbon dioxide 0.3 per cent. The heart rate increased from 88 to 97. The test was stopped because of respiratory distress. There was dizziness and headache but no precordial pain. There were no electrocardiographic changes.

Case 31, Coronary group I, male, fifty-one years old. Three months before the patient was in Beth Israel Hospital with an attack of coronary occlusion. He had never had symptoms of heart disease prior to the attack. Since the closure he suffered from shortness of breath and sharp attacks of pain starting in the left elbow and radiating up the arm to the shoulder and then down the left side of the chest. The pain was brought on by excitement or exertion. The pain was relieved by nitroglycerin. The apex of the heart was in the fifth interspace, 10 cm. to the left of the midline. There was a rough systolic murmur heard best over the aortic area. Blood pressure: 106/76. Electrocardiogram: negative. Diagnosis: *Healed infarction of the heart*. Anoxemia: The experiment lasted ten minutes. The oxygen reached 8.6 per cent, the carbon dioxide 0.1 per cent. The heart rate increased from 81 to 103. The test was halted when the patient developed an attack of pain in the left elbow which radiated to the shoulder and down the left side of the chest. This attack was identical with the patient's usual attacks. It was relieved within a minute after air was admitted. In the last three minutes the electrocardiogram showed a drop of 1 mm. in the S-T segment of Lead I and an elevation of 1 mm. in the S-T segment of Lead III.

Case 32, Coronary group I, male, sixty-five years old. For six years the patient had suffered from fatigue, shortness of breath, belching, and pain at the upper end of the sternum. The pain was pressing in nature and radiated to the left arm. It was brought on by exertion and heavy meals and was relieved by nitroglycerin. The apical impulse was not palpable. The heart sounds were of good quality. There was a systolic murmur heard best over the aortic area and another heard best at the apex. Blood pressure: 160/80. Electrocardiogram: Repeatedly negative until one month ago when the T-wave of Lead I became inverted. Diagnosis: *Coronary artery disease*. Anoxemia: Duration eight and one-half minutes. Oxygen level reached 11.2 per cent, carbon dioxide 0.2 per cent. The heart rate increased from 83 to 100. The electrocardiogram showed flattening of the T-wave in Lead I in the last few minutes. The experiment was stopped when the patient developed shortness of breath. He developed a mild attack of precordial pain in the last minute. The pain disappeared as soon as air was admitted.

Case 38, Coronary group I, male, forty years old. The patient, a physician, gave a history of attacks of anginal pain commencing ten months previous to the first examination. The attacks started with a feeling of oppression under the sternum. The pain then radiated to the left shoulder and occasionally to the neck and always down the left arm. The last attack was a week ago after climbing one flight of stairs. The attack lasted about a minute. Nitroglycerin afforded relief. Attacks followed slight exertion. The heart was rapidly pulsating. It was regular. The heart sounds were of good quality and there were no murmurs. Blood pressure: 138/92. Fluoroscopy: Heart and aorta normal. Electrocardiogram: Negative on the first examination when the anoxemia test was performed. Six months later, the tracing showed a flat T-wave in Lead I and an inverted T-wave in Leads II and III. Diagnosis: *Coronary artery disease*. Anoxemia: The experiment lasted eleven and one-half minutes, the oxygen reached 9.4 per cent, the carbon dioxide 0.5

per cent. The heart rate increased from 97 to 108. The electrocardiogram showed a decrease in the height of the T-wave in Leads II and III. During the last minute, the patient developed an attack of pain, identical with his usual attacks, which caused him to terminate the experiment. The pain was not relieved when air was admitted and after one and one-half minutes, amyl nitrite was administered, which gave prompt relief. During the control period the patient was slightly short of breath at intervals but otherwise perfectly comfortable.

Case 41, Coronary group II, male, forty-four years old. Seven weeks before the patient developed a squeezing pain across the chest accompanied by a choking sensation and shortness of breath. The first attack came on while the patient was walking and attacks recurred daily for five days. He was compelled, with each attack, to stop walking. After ten minutes he would be able to go on. The patient could walk slowly as far as he liked but he was unable to walk quickly or up stairs because of the attacks. The heart sounds were of good quality. There were no murmurs. Blood pressure: 150/85. Fluoroscopy: The heart was not enlarged. There was slight rounding of the left ventricle. The aorta was not dilated and the lungs were clear. Electrocardiogram: negative on several occasions. Diagnosis: *Probably coronary sclerosis*. Anoxemia: Duration eighteen and one-half minutes, oxygen level reached 8.8 per cent, carbon dioxide 0.05 per cent. The heart rate increased from 90 to 110. The T-wave of Lead I became flattened. The test was halted when the patient developed an attack of pain in the chest. The pain came on in the last half minute. It was identical with his usual attacks. The pain stopped within a few seconds after air was admitted. During the control period, the patient was completely comfortable.

Case 42, Coronary group II, male, fifty-two years old. The patient complained of pain across the nipples for two months. One year ago he had the same sort of pain. The pain would come on when the patient walked or climbed stairs. There was tingling of the left arm with the chest pain. When the patient stopped walking, the pain disappeared. The heart sounds were slightly distant but otherwise normal. There were no murmurs. Blood pressure: 130/70. Fluoroscopy: Rounding with slight hypertrophy of the left ventricle. The aorta was elongated but not widened. The lungs were clear. Electrocardiogram: Negative. Diagnosis: *Probably coronary sclerosis*. Anoxemia: Duration seventeen minutes. Oxygen 9.8 per cent, carbon dioxide 0.7 per cent. The heart rate increased from 70 to 88. There were no electrocardiographic changes. In the last minute the patient developed precordial pain accompanied by tingling in the left wrist. This disappeared within a few seconds after air was admitted. During the control period, the subject was perfectly comfortable.

Case 43, Coronary group II, female, thirty-nine years old. Four months before the first examination, the patient was laid up with a mild attack of grip. Ten days later, on walking, she felt a pain across the chest. Since that time, there were many attacks. The pain came on after walking about half a block. The pain was burning. It radiated across the chest and down both arms into the elbows. When severe, it radiated to the fingers of both hands. The pain was worse in cold weather. It was especially bad walking against the wind. Climbing stairs precipitated attacks. The pain was accompanied by shortness of breath. At the age of seventeen years the patient was told that she had inflammatory rheumatism. The heart was regular and rapid. There was a systolic murmur at the apex, louder on exercise. Blood pressure: 140/90. Fluoroscopy: The heart was not enlarged. There was no evidence of mitral disease. Electrocardiogram: Negative. Diagnosis: *Impaired coronary circulation*. Anoxemia: The test lasted sixteen minutes, the oxygen reached 9.6 per cent, the carbon dioxide 0.02 per cent. No electrocardiograms were taken.

In the last minute the patient developed pressure on the chest, "like the pains I get when I walk." The pain increased in severity so that the subject signalled to halt the test. The pain lessened as soon as air was admitted, but it did not disappear for three minutes. During the control period the patient was perfectly comfortable.

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INDUCED GENERAL ANOXEMIA CAUSING S-T DEVIATION IN THE ELECTROCARDIOGRAM*†

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IT WAS reported in a previous communication¹ that the subjective response to anoxemia of individuals with angina pectoris differed from the response of control subjects. Subjects with angina pectoris developed precordial pain during exposure to atmospheres of low oxygen tension; control subjects did not. We felt that there might appear during anoxemia an objective finding which would aid in distinguishing between the two groups. We therefore investigated the electrocardiographic changes during anoxemia in subjects with and without angina pectoris.

METHOD

Anoxemia was induced by rebreathing, with the technic described in a previous publication.¹ Thirty-eight individuals were studied. The subjects were divided into two groups. The control group consisted of 14 individuals without clinical evidence of impaired coronary circulation; the other group consisted of 24 individuals with angina pectoris.

A three-lead electrocardiogram was taken before the subject had begun to rebreathe. Two minutes after the start of rebreathing, records of the three leads were taken in rapid succession. As a rule, one could take a strip about 7 inches long (seven seconds) of each lead and finish within thirty-five or forty seconds. Tracings were taken every two minutes for the first ten minutes, then every minute until the close of the experiment. If the patient became cyanotic or showed signs of anoxemic distress during the first ten minutes, tracings were taken every minute after that time instead of waiting for ten minutes to elapse. One minute after the period of anoxemia another set of tracings was taken, and again, in most instances, three minutes after the anoxemic period had come to a close.

At the end of the experiment a sample of air was taken from the rebreathing chamber and its oxygen content determined with the Haldane apparatus.

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If the resistance of the patient was high, overshooting of the galvanometer might occur, and produce after a high R-wave, a downward deviation of the R-T (S-T)* segment which is only artefact. In order to obviate such distortion, we took care that the resistance of the patient was 2,000 ohms or less by cleansing the skin with alcohol,

TABLE I
SUMMARY OF RESULTS OF ANOXEMIA

CASE NUMBER	GROUP	OXYGEN IN INSPIRED AIR	PAIN	S-T DEVIATION
1	Control I	8.1%		+
2	" I	8.9		No Ecg.
3	" I	7.8		No Ecg.
4	" I	6.1		
5	" II	6.4		+
6	" II	8.7		
7	" II	7.8		No Ecg.
8	" II	8.3		+
9	" II	8.1		
10	" III	6.8		No Ecg.
11	" III	8.8		
12	" III	6.4		No Ecg.
13	" III	8.1		
14	" III	7.5		
15	" III	8.5		
16	" III	8.8		
17	" III	7.0		
18	" III	10.3		No Ecg.
19	" III	9.6		
20	" III	7.7		
21	Angina I	8.0		
22	" I	9.8		+
23	" I	8.1		
24	" I	9.4		
25	" I	7.9		
26	" I	6.4		+
27	" I	7.9		
28	" I	6.4	+	
29	" I	8.6	+	
30	" I	8.4	+	
31	" I	8.6	+	+
32	" I	11.2	+	
33	" I	11.2	+	+
34	" I	12.9		
34	" I	8.8	+	+
35	" I	9.9	+	
36	" I	7.4		+
36	" I	9.6	+	
37	" I	7.1	+	
38	" I	9.4	+	
39	" I	8.7		No Ecg.
40	" II	5.9	+	+
41	" II	8.8	+	
42	" II	9.8	+	
43	" II	9.6	+	No Ecg.
44	" II	8.4	+	
45	" II	8.9	+	+
46	" II	9.1	+	

*S-T will be used throughout for convenience.

rubbing the skin, using hot bandages, and preventing the salt solution from drying by wrapping rubber pads around the bandages.

RESULTS

Three of 14 control subjects developed changes in the S-T segment. Of these three, two were patients without precordial pain but with evi-

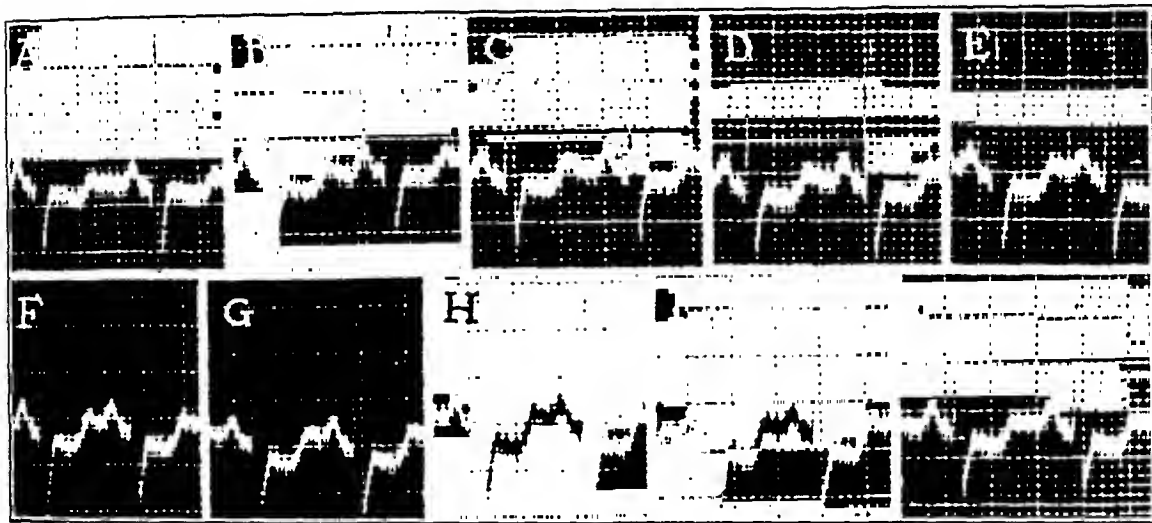


Fig. 1.—Lead II of Case 33.

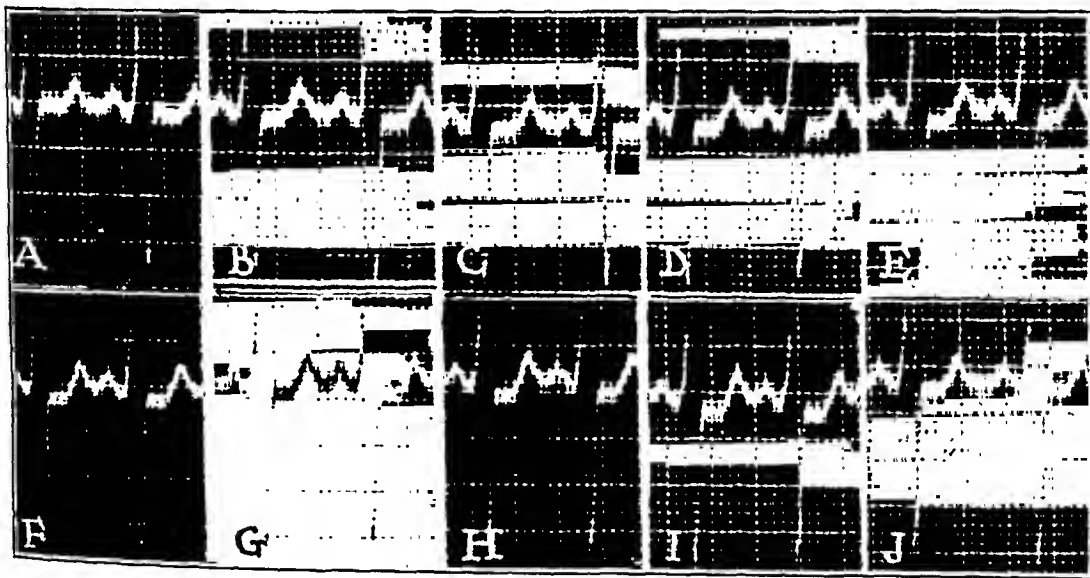


Fig. 2.—Lead III of Case 33. A, Before anoxemia; B, after one minute of re-breathing; C, two minutes; D, three minutes; E, four minutes; F, five minutes; G, six minutes; H, seven minutes; I, eight minutes; J, one minute after the end of the anoxic period. Note the depression of the S-T interval after the first minute of re-breathing.

dence of myocardial disease, and one was a man of twenty-six years without signs of heart disease. Eight of 24 subjects with angina pectoris developed a deviation of the S-T segment.

The relationship between precordial pain¹ and the S-T change is shown in Table I. Of the 24 anginal subjects whose electrocardio-

grams were taken during induced anoxemia, eight developed distortion of the S-T interval. Five of these eight developed pain as well. In 12 anginal subjects pain appeared but no S-T change.

The change in the S-T segment appeared toward the end of the rebreathing period, as a rule, and became more marked as the degree of anoxemia increased. As soon as the anoxic period was ended, the phenomenon began to disappear. We did not follow the full course of its disappearance, but in most instances the S-T interval reached its original level within three minutes, often within one minute.

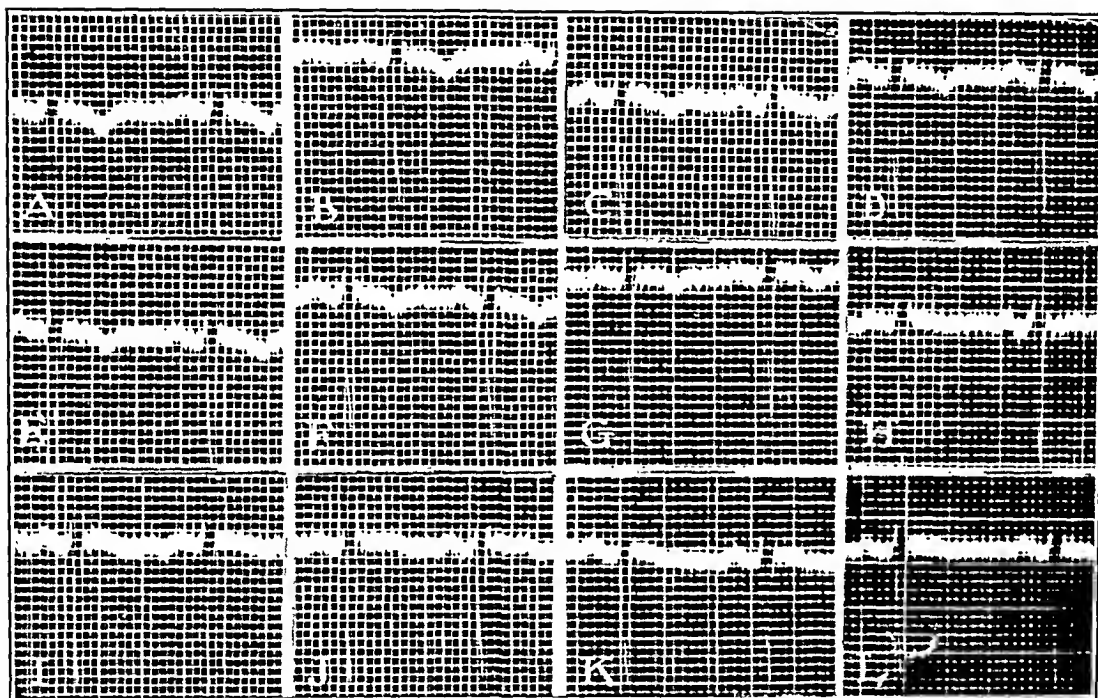


Fig. 3.—Lead III of Case 31. *A*, Before anoxemia; *B*, after one minute of rebreathing; *C*, two minutes; *D*, three minutes; *E*, four minutes; *F*, five minutes; *G*, six minutes; *H*, seven minutes; *I*, eight minutes; *J*, nine minutes; *K*, ten minutes; *L*, one minute after the end of the anoxic period. Note the elevation of the S-T segment in the eighth, ninth, and tenth minutes.

The S-T deviation was always downward, except in one case which showed an upward deviation in Lead III (Fig. 3). The deviation of the S-T interval from the isoelectric line varied from 0.5 to 2.5 mm. In two cases the distortion appeared only in Lead II, in one case only in Lead III, in four cases in Leads I and II, in two cases in Leads II and III, and in one case in all three leads. In one case there was a downward deviation in Lead I and an upward deviation in Lead III. Figs. 1 to 5 illustrate representative tracings.

The oxygen content of the inspired air varied in those showing S-T changes from 5.9 to 8.9 per cent, with two exceptions. Cases 22 and 33 did not fall below 9.8 and 11.2 per cent respectively. The last two

figures were in cases of intraventricular block. Oxygen levels reached by those exhibiting no distortion of the S-T interval varied from 6.1 to 12.9 per cent (Table II).

One patient (Case 34) developed S-T deviation when he reached an oxygen level of 8.8 per cent, but when on a previous occasion the final level was 12.9 per cent, no change appeared. Similarly, in Case 36, no change in the S-T segment appeared in one experiment when the oxygen level fell only to 9.6 per cent, but in another experiment deviation appeared with a final level of 7.4 per cent.

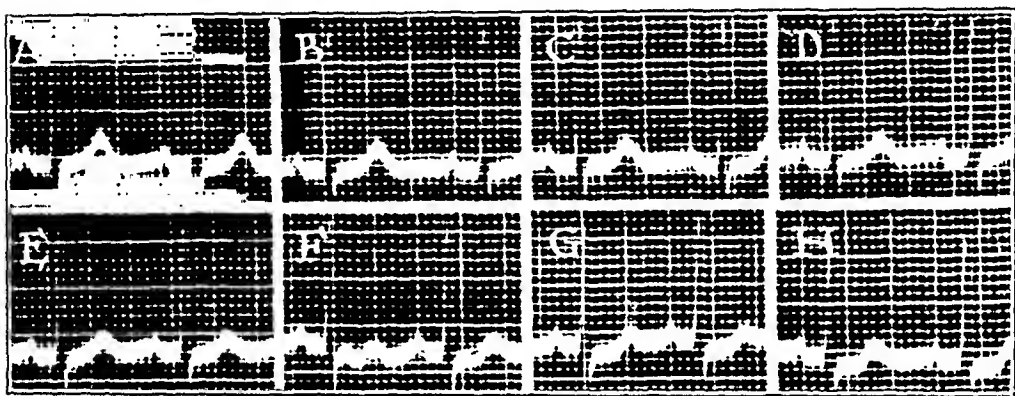


Fig. 4.—Lead I of Case 40.

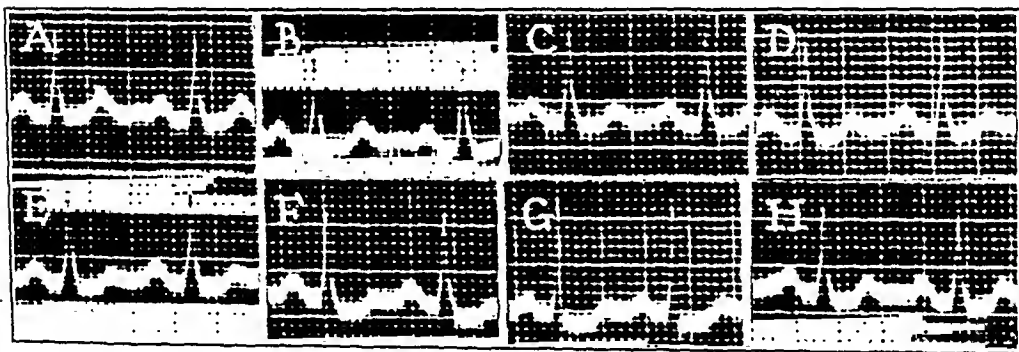


Fig. 5.—Lead II of Case 40. A, Before anoxemia; B, after ten minutes of rebreathing; C, fifteen minutes; D, seventeen minutes; E, eighteen minutes; F, twenty minutes; G, twenty-one minutes; H, one minute after the end of the anoxic period. Note the depression of the S-T segment in the seventeenth minute and thereafter.

We endeavored in one instance to reproduce the S-T change that appeared during anoxemia in a case with intraventricular block. First, we tried the effect of inhaling mixtures rich in oxygen and carbon dioxide. Second, we administered atropine intravenously to produce a tachycardia. Third, we gave epinephrin subcutaneously for its reputed ability to increase the work of the heart. Fourth, we administered pitressin for its vasoconstrictor effect. Fifth, amyl nitrite was tried for its vasodilator action. Oxygen and carbon dioxide caused no side actions; atropine caused tachycardia, dryness of the mouth, and mydriasis; epinephrin caused palpitation and a tremor of the hands; pitressin produced a greenish pallor and called forth a desire

TABLE II
FINAL OXYGEN CONTENT OF INSPIRED AIR IN SUBJECTS THAT DID AND DID NOT DEVELOP S-T DEVIATION

CONTROL GROUP		ANGINA GROUP	
S-T CHANGE	NO CHANGE	S-T CHANGE	NO CHANGE
6.4%	6.1%	5.9%	6.4%
8.1	7.5	6.4	7.1
8.3	7.7	*7.4	7.9
	8.1	8.6	7.9
	8.1	†8.8	8.0
	8.5	8.9	8.1
	8.7	9.8	8.4
	8.8	11.2	8.4
	9.6		8.6
			8.8
			9.1
			9.4
			9.4
			*9.6
			9.8
			9.9
			11.2
			†12.9
Average	7.9	8.4	8.9

Average for all showing S-T changes - - - - - 8.2%
Average for all not showing changes - - - - - 8.7

*, † Indicates same case.

to defecate; amyl nitrite produced flushing of the skin and headache; but none caused a deviation of the S-T segment.

DISCUSSION

It is clear that the electrocardiographic change in question, namely, S-T deviation, occurs in individuals with normal coronary circulation as well as in individuals with impaired coronary circulation. But the change appeared more frequently, in our series, in those with impaired coronary circulation. It is probable, too, that hearts with impaired circulation are more sensitive to oxygen lack than are normal hearts, that the S-T distortion appears at a higher oxygen tension in the ischemic heart than in the normal. This is indicated in the two cases (22 and 33) of intraventricular block, mentioned above, in which S-T deviation appeared at a comparatively high oxygen level.

Electrocardiographic changes other than S-T deviation appear during anoxemia. These changes, such as flattening of the T-wave and increase in the height of the P-wave, were described by Greene and Gilbert^{2, 3} and Ward and Wright.⁴ Lewis and Mathison,⁵ Mathison,⁶ von Ángyán,⁷ Lewis, White and Meakins,⁸ Haggard,⁹ and Colvin¹⁰ reported auriculoventricular heart-block during asphyxia. Mathison,⁶ Greene and Gilbert,¹ and Resnik¹¹ observed the same finding during induced anoxemia. None of these authors made note of S-T distortion. However, Kountz and Gruber¹² described deviation of the S-T inter-

val in dogs during general anoxemia and Kountz and Hammouda¹³ reported the same finding in perfused dogs' hearts that had been asphyxiated. Katz and Hamburger¹⁴ have noted this finding in 20 normal persons during anoxemia.

The changes in the S-T segment that appear during anoxemia are identical with those observed during attacks of angina pectoris.¹⁵⁻²¹ Similar findings have been noted in persons with rheumatic fever,²²⁻²⁶ coronary occlusion,²⁷⁻³⁵ uremia,³⁶ and pneumonia.³⁷⁻⁴⁰ Pericardial effusion, clinical and experimental, has resulted in deviation of the S-T interval.⁴¹⁻⁴⁵ Similar changes have been described following experimental occlusion of the coronary arteries⁴⁶⁻⁵⁵ and of the coronary sinus.⁵⁶ Feil, Katz, Moore, and Scott⁵⁷ found no characteristic change in the S-T interval following the ligation of the descending branch of the left coronary artery in dogs, but when, in addition, they ligated the inferior vena cava typical deviations appeared. Distortion of the S-T segment has been produced by direct injury to the myocardium or by the injection of caustic substances into the myocardium.⁵⁸⁻⁶² Electrocardiograms taken during experimental anaphylaxis have shown this change.⁶³ Similar findings have been noted after the administration of epinephrin,⁶⁴ insulin,⁶⁵⁻⁶⁹ digitalis,^{70,71} and pitressin.^{72, 73}

SUMMARY

Electrocardiograms of 38 individuals were taken during the induction of progressive anoxemia. Eleven subjects developed deviation of the S-T segment. Eight of the 11 suffered from angina pectoris, three did not. The deviation of the S-T segment was usually downward but in one case was upward. The degree of deviation was related to the degree of anoxemia. No qualitative electrocardiographic finding appeared during anoxemia that will serve to distinguish between individuals with unimpaired coronary circulation and those with impaired coronary circulation.

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ANGINA PECTORIS. A PLEA FOR GREATER OPTIMISM IN PROGNOSIS

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THIS is a plea for the more cautious use of the terms "angina pectoris" and "coronary thrombosis" and for a more optimistic attitude toward patients included in these categories. In the mind of the average layman the first of these phrases has for many years carried the implication of complete and incurable invalidism and sudden death, and recently the second has entered common parlance and in the view of the man in the street holds an equally sinister significance.

Physicians make use of the term "angina pectoris" so frequently that it seems as if almost any chest discomfort may be labeled with this diagnostic tag. It is used nearly as nonchalantly as was the term "malaria" before the days of the discovery of the plasmodium and with almost as little thought as is employed today in assigning respiratory infections and abdominal disturbances to that all-embracing term "influenza." In the last decade we doctors have become, as a recent writer¹ has expressed it, "coronary conscious," and apparently we are now swinging from the Scylla of nonrecognition to the Charybdis of easy going, loose thinking in making this diagnosis. This is particularly regrettable since such a statement conveys to the patient the impression that he is suffering from what is generally regarded as a grave heart condition from which recovery is impossible, which is totally incapacitating and in which death may be imminent at any moment. These labels differ from "malaria" and "influenza" in that these latter conditions are commonly regarded rather lightly by the patient and carry a reasonable assurance of a complete cure.

One would think from the literature, from discussions at medical gatherings and from conversations with many members of the profession that the diagnosis of "coronary thrombosis," and the proper selection of individuals who should be grouped as suffering from "angina pectoris" are simple matters. This I believe is a very erroneous idea.

It is not, in my experience, uncommon to see patients who have been told that they have "angina pectoris" or "coronary thrombosis" who present no objective evidence whatever of an organic defect of the heart or aorta. The heart is of normal size and the sounds are of good quality; there are no murmurs. No friction sound has been heard. As far as can be determined by physical examination or x-ray

studies, the aorta is normal. The blood pressure is normal. There is no definite record of an abnormal heart rate, fever or leucocytosis. The electrocardiogram is normal. The whole evidence offered is a statement of his subjective sensations made by the patient. In many instances an acute attack has not even occurred under the observation of a physician. Many members of this group have a history and other evidences of a highly organized nervous system, and they react with abnormal violence to minor physical or mental stimuli. The evaluation of this subjective evidence is sometimes made even more difficult by the fact that some of these individuals have a subconscious desire to secure sympathy and for this reason would gladly be regarded as chronic invalids, others depressed by the condition of their business affairs would not be sorry to secure financial relief from the operation of a disability clause in an insurance policy. Such conditions undoubtedly act as strong incentives which, consciously or unconsciously, tend to color the story which may be the only evidence upon which the diagnosis must rest.

Let me make myself clear. I do not contend that a man who presents such a picture may not be suffering from "angina pectoris" or even from "coronary occlusion," but I do insist that under such circumstances the true evaluation of the condition is at times most difficult, that a snap diagnosis is not justified and that one should reach a decision only after prolonged and careful study and a most thoughtful analysis of the available evidence.

In considering the condition of patients in whom a heart defect is suspected (this applies also to those with a definitely established diagnosis of heart disease), the psychic element is too often neglected. Most persons are deeply disturbed by any suggestion that they have an abnormal heart. As Conner² has expressed it, "the reaction to doubt concerning the integrity of the heart seems to be much more violent and profound than is the case with any of the other internal organs." This is particularly in evidence in patients who are nervously unstable, who have a morbid concern for their state of health, who are easily subject to suggestion and are prone to introspection, but is not limited to these groups, for the nonemotional, well balanced type of individual may be intensely shocked by an intimation that there is an imperfection in this organ, of such vital importance to his health and well-being. There are many sources from which these psychic traumata may come; common among these are the various sensations in the region of the heart of which the patient is conscious, such as pain and palpitation, tachycardias and arrhythmias, the sudden death of a close friend or a member of the family which has been attributed to heart disease, the injudicious statement of a life insurance examiner, or most often of all, the unguarded verdict of the physician who has been called in for an emergency.

The caution which one should employ is illustrated by the following case:

Mr. F. was a man of fifty-five years, who in January, 1927, came to see me complaining of paroxysmal attacks of severe precordial pain radiating to the left arm, which had been troubling him for six weeks. The pain came on only upon walking and stopped after resting for a minute. His descriptions of the paroxysm were in detail quite characteristic of attacks of "angina pectoris." Physical examination showed nothing abnormal except that the heart sounds were a little indistinct and the fluoroscopic findings suggested an aorta that was a trifle wide for a man of his build. The blood pressure was normal. The electrocardiogram was normal. The urine showed a heavy trace of albumin and a few red blood cells, which had been found off and on over a period of twenty years. He was of a high strung, nervous type, worried by heavy business responsibilities. He was paralyzed with fear by his physical condition, expecting a fatal termination at any moment and was preparing to retire from business to resign himself to the life of an invalid. Further questions brought to light the story of an intimate friend who had suffered from "angina pectoris" and had died suddenly ten days before our patient had first noticed his substernal pain. Mr. F. had always used alcohol and tobacco in considerable quantities; he had discontinued the use of both soon after his first attack of pain, but he still continued the use of strong coffee, three to five cups a day. Every effort was made to reassure him; he was advised against closing up his business which he could ill afford to do, was told to take a complete rest in Florida for six weeks and was advised to discontinue the use of coffee. Subsequent events proved that the advice which had been given (it must be confessed with considerable mental reservation) was justified. In the course of a few weeks the pain entirely disappeared, and at the present time he is perfectly well, living a normal life and following his usual business activities.

The difficulties of formulating a correct prognosis in an individual patient is generally recognized. To the physician, statistics may be of value in orienting his general ideas in regard to this group of patients as a whole, but he will be led into a quagmire if he attempts to apply the figures thus obtained to the individual case. Even the life insurance companies (for which the statistical method has made sound business possible) have realized the inadequacy of this method when dealing with the individual claiming disability for "angina pectoris" and "coronary thrombosis."

Statistics and dramatic experiences with sudden death occurring soon after an examination which had revealed very little objective evidence of an organic lesion, have developed a pessimism in physicians which directly or indirectly is all too often conveyed to the patient, destroying his morale and inducing an apprehension devastating to his career.

If we are to be of real service to our patients, this situation demands a guarded optimism; pessimism is out of place. We have legitimate grounds for assuming a hopeful attitude in the individual case. Granting that an accurate prognosis for the individual is impossible, we

still are justified in assuming that a given patient is likely to complete years of useful living and may not be the one limited to a brief period of suffering and invalidism. I feel warranted in taking this attitude, since I am seeing from time to time a very considerable number of patients in whom I feel that the history, physical signs, and course of events observed over a long period have warranted me in making a definite diagnosis of "coronary thrombosis" or of grouping them under the syndrome of "angina pectoris," and who are living ten or fifteen years after the first attack. An occasional patient has been entirely relieved of symptoms of every kind; some are doing full work with only occasional discomfort; others are living a life of limited activity with a modest amount of work and many interlarded hours of pleasure. Fifteen years of even a very restricted life for a man fifty-five or sixty years of age is not so bad, and this may be the lot of any one of these cases.

A case of interest in this connection is that of a man sixty-nine years of age who came under my care because of a severe lobar pneumonia which proved to be fatal. In securing his history he gave me a very vivid description of having had when fifty-one years of age a severe and prolonged attack of substernal pain and other symptoms which strongly suggested the picture of "coronary thrombosis." Following this he had a number of attacks of substernal pain which gradually became less severe and less frequent, until at the end of two years they entirely disappeared. During this period he was able to do a moderate amount of work, and after the complete subsidence of the pain he gradually resumed full activities and was able to carry on a large and important law practice. After the patient succumbed to pneumonia, the autopsy showed a heart that was slightly enlarged, with some calcification of the coronaries and near the lower part of the left ventricle an area of fibrosis and calcification, evidently the residuum of an old infarct, thus verifying the lesion which his history had suggested. The impressive part of this picture is the fact that this heart was able to recover from such an insult sufficiently to support life for sixteen years without symptoms referable to the circulation.

A very similar case of a man who had an attack of "coronary thrombosis" at the age of sixty-three years, and thereafter lived for seventeen years with periods of remarkable physical activity, has recently been reported by White.³ In their study of "coronary thrombosis," Conner and Holt⁴ report one patient as living and well seventeen years after the original attack and several patients who had lived for over ten years. White and Bland⁵ have had three patients under observation with anginal attacks for twenty years or more. In his discussion of "coronary occlusion," Krehl⁶ says "such a lesion is perfectly compatible with the continuation of life . . . he lives on and may never suspect what an abyss he has escaped."

It is helpful at times, to lay aside one's personal experiences, such as have been presented in this paper, and to review the facts presented

by an acute, independent observer who is unbiased by the impressions which have been gradually forcing themselves on one's own mind. I have recently analyzed the case histories published by Mackenzie⁷ in his book *Angina Pectoris*. He records the histories of 147 patients which he classified as "primary angina pectoris." Of these, one man was living thirty-one years after his first attack, still following his trade of a joiner; three had lived twenty-five years or more; one had lived twenty years; seven for fifteen years or more, and twenty-one for ten years or more. This makes a total of 33 individuals who lived for more than a decade after the first paroxysm of pain, and, at the time the report was published, 16 of them were still alive. That the patients of this group of 33 did not die young is indicated by the fact that the average age of those still alive was sixty-four years, and the average age of those dead was seventy-one years. It should be noted also that in a number of these cases death was due, not to angina, but to such conditions as carcinoma, gangrene of a leg, apoplexy, etc. It is further recorded that in the periods following a definite classification as cases of "angina pectoris" a number of these patients were able to play golf without discomfort, one man was "shooting" as had been his custom, there were a trained nurse and a supervisor of nurses both doing regular hospital work, a builder active in his vocation, a man whose travels took him to Florida, Mexico, Argentina and across the Andes at an elevation of 10,000 feet, another who made business trips to Russia, China, Australia and America. There were eight physicians, five in active practice and the others doing a limited amount of work.

This discussion has intentionally avoided an attempt to consider in separate groups cases of coronary thrombosis with anginal symptoms and cases of angina pectoris associated with other pathological or toxic factors. Such a differentiation can often be made promptly; in other instances it may be made after prolonged observation and study, at times it will be made only at the post-mortem examination or perhaps not at all.

From the standpoint of the physician the syndrome of "angina pectoris" should always be taken seriously, but this label should never be attached without due thought and study. Whenever possible this term should be withheld from the patient, for it hangs above him like the sword of Damocles destroying all the possible joys of the banquet of life. As a rule, much less terrifying phrases can be used to secure the necessary cooperation. The prognosis should always be tintured with hope, for any given individual may be the one to whom is allotted, as in the cases cited above, years of reasonable activity and comfort.

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ARTERIAL HYPERTENSION AND ARTERIOSCLEROSIS ASSOCIATED WITH RAYNAUD'S SYNDROME*

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PATIENTS with arterial hypertension, with or without clinically detectable arteriosclerosis, complain at times of periodic attacks of coldness of the fingers and toes, associated with pallor or cyanosis, with pain or paresthesia, and with temporary weakness of the hands and feet. The attack is usually precipitated by low temperature of the surroundings or by work; emotions play no rôle, in our experience. Spasm of other parts of the vascular tree is not necessarily present. In mild form this syndrome is not infrequent; in severe form it is comparatively rare. Its clinical characteristics resemble strikingly those of classical Raynaud's disease.

So far as we are aware, no information is available as to the physiological mechanism of this syndrome. This communication presents observations on a patient who exhibited severe attacks, in the hope that the study will throw light on the nature of the attack.

REPORT OF CASE

A sixty-eight-year-old, retired railway worker entered the hospital on October 8, 1930, with the complaint of numbness and blanching of the hands. Ten months previously he began to have attacks of numbness and tingling of the two small toes of the left foot, coming at any time, but more often after exertion and in cold weather. At first the attacks would last but a few minutes, but later they increased in number and severity until he was having several daily. He did not know whether there was any change in the color of the skin associated with them. His feet were cold most of the time. Nine months before entry he began to have similar attacks in the hands, which almost always occurred bilaterally. He first experienced numbness of the fingers, which would become pale or blue. After from ten to fifteen minutes the pallor or cyanosis would be replaced by pinkness, and the numbness by tingling. Exposure to cold and undue exertion seemed to be the chief precipitating factors; emotions had no effect. Between attacks his hands were at times slightly blue and cold.

For five months he had noticed that he became fatigued easily, and was subject to increasing dyspnea on exertion. Family and past histories were irrelevant.

Physical examination showed an enlarged heart and supracardiac dullness, with normal sounds except for an accentuated aortic second sound. The arterial blood pressure was 184 mm. Hg systolic and 102 mm. diastolic. There was marked peripheral sclerosis, with tortuosity and beading of the vessels of the extremities, but good pulsation of the dorsalis pedis arteries was noted. It was observed that on

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exposure to cold his hands and feet became cyanotic and cold, while in a warm room they were of normal color and warmth. The results of the remainder of the examination were unessential.

The laboratory tests showed nothing abnormal except for a secondary anemia of 3.5 million red blood cells per cubic millimeter, with 51 per cent hemoglobin.

CLINICAL STUDIES

Induction and Nature of Attacks.—When the hands were placed in water at 22° C., no change was observed. Putting the hands in water at 18° C. for five minutes usually precipitated an attack. A temperature of 15° C. always precipitated an attack, and this temperature was ordinarily employed in the subsequent work in producing attacks. Immersion in water at 12° C. or lower produced either no attack or a very transitory one, to be quickly replaced by a pink flecking associated with increase in skin temperature. A given stimulus (cold) usually produced a more intense and lasting attack in the right hand than in the left, although the minimal stimulus was about the same for the two hands. The patient subjectively had previously noted no difference in the character of the attacks between the two hands.

In these induced attacks the fingers were chiefly involved, the thumbs and the palms only slightly. On removing the hand from the cold water to room temperature (24° to 26° C.) one or more fingers were usually very pale and blanched, while the others were cyanotic. After a few minutes the pallor of the fingers was often replaced by intense cyanosis. The attacks would last from twenty to forty minutes after removal of the hand from the cold water and would clear gradually. The end of the attack was indicated at first by small mottled areas of pinkness which spread and increased in number until the whole finger was pink. Finally, the entire hand would become pink and warmer than normal, as indicated by skin temperature measurements. Occasionally, usually after prolonged immersion in water between 15° and 18° C. or in water considerably below 15° C., one or more fingers or the whole hand would be pink but cold; later they gradually changed to a pale or cyanotic color; such an attack ended with pink and warm skin. The same hand did not always go through quite the same sequence in developing attacks. Producing an attack in one hand by putting it in water never caused one in the other hand through vasomotor cross reflexes, and immersion of the elbow alone or of the arm above the hand in cold water did not cause an attack over the immersed areas or in the hand. None of the above-described experiments produced a change in the brachial and radial pulsations.

When an attack with blanching of a finger had been induced, holding the hand in a dependent position for several minutes or the application of a venous tourniquet for not more than five minutes did not relieve the blanching.

Ulnar anesthesia by infiltration of the nerve at the elbow with novocaine had no influence either on the production or on the nature of the attacks.

Observations on the Capillaries.—The purpose of these observations was to correlate the morphological state of the capillaries of the nail bed and the character of the blood flow with the appearance of the fingers. A special microscope was used for these observations, and each observation was repeated several times.

When a finger was blanched, very few capillaries were visible, and the venous ends of the capillary loops were unusually narrow. There was no flow through the capillaries. When the finger was cyanotic, numerous capillaries were visible, full of blood, but there was either no flow or at most a slow and intermittent flow. When a finger was pink but cold, the capillaries could be observed in great number but the flow was either absent or extremely slow. Often red blood cells stagnating in clumps were visible. When the finger was pink and warm, many capillaries were open and the flow through them was much more rapid than in the normal state.

It is apparent that a bright pink color of the skin may be associated with either of two diametrically opposed states of the blood flow: either very rapid capillary blood flow with normal tissue metabolism, or sudden slowing of the blood flow in the presence of unusually low tissue metabolism. This latter state, occurring in chilled extremities, allows the red blood corpuscles to contain a high content of oxygenated hemoglobin in the venous ends of the capillary loops and in the subcapillary venous plexuses which are responsible for skin color.

The Effect of Vasodilator and Vasoconstrictor Substances.—The following substances were given in doses sufficiently large to produce their full systemic effect, but in no case did they either relieve or alter an attack already present or prevent the occurrence of one when they were administered before and during the induction of the attack:

Histamine phosphate, 1:100,000 intravenously in dosages up to 10 c.c. (0.1 mg.) per minute; *acetylcholine hydrobromide*, 1:50, intravenously in dosages up to 3 c.c. (60 mg.), per minute; *sodium nitrite* by mouth in successive doses of 3 and 2 grains fifteen minutes apart.

Epinephrine, 5 c.c. of 1:30,000 (0.16 mg.) injected into the right antecubital artery in from two to three minutes. Following this there was an intense constrictor effect over the whole forearm and hand, with pallor lasting about fifteen minutes to be replaced by intense blushing. At this stage a typical attack was produced by immersion in cold water.

One dose of 25 million killed typhoid bacilli intravenously was followed by a chill and febrile reaction. Immediately following this,

when the hand was immersed in the usual manner, it was pink but cold, and remained so for twenty-five minutes, after which it gradually became cyanotic and then normal. Subsequently, spontaneous attacks occurred with their usual frequency.

DISCUSSION

It is known that in the clinical course of arterial hypertension or of arteriosclerosis certain vascular areas may become irritable, leading to attacks of spasm. Such spasm is claimed to play a rôle in the precipitation of cerebral crises, periodic cranial nerve palsies, angina pectoris, abdominal crises, intermittent claudications, and other clinical manifestations. The finer mechanism of these regional vascular disturbances is not known, for they have been but incompletely studied. The syndrome presented by this patient is of the same type of vascular disorder. The vessels of the fingers, and presumably of the toes, exhibited a vasospastic tendency. The fact that the cold had to be applied locally to exert its effect and that ulnar anesthesia did not influence the attacks, suggests that the irritability lies in the arterial wall itself and not in the nervous tissue. The finding that histamine and acetylcholine not only did not improve the attacks but failed even to prevent them, also suggests that the morbid changes were located in the vessel wall proper. The vasospastic tendency of the vessels was intense, for administration of sodium nitrite and typhoid bacilli, powerful dilators acting on the muscular coat, did not influence the attack.

The observations of empty capillaries or capillaries open and filled with stagnating blood and of low skin temperature indicate that the vascular occlusion must have developed proximal to the capillaries, in the arterial vessels, i.e., in small arteries or arterioles or in both. The fact that the induced venous stasis and dependent position of the arm had no appreciable effect on the pale color and coldness of the fingers indicates that the small venules were also in a state of active constriction. We have presented evidence that the venules of the skin are sensitive to chemical stimuli.¹

Some of the observations, including the critical temperature for the precipitation of attacks, are in harmony with those described by Lewis on patients with Raynaud's disease.² While the classical Raynaud's disease appears in youth or in early adult life and emotions may play an important rôle, in the case studied and in others observed by us, this syndrome develops in late middle life or in old age after arterial hypertension has existed for several years. Whether arterial hypertension leads directly to irritability of the arterial vessels of the fingers or toes, or whether such a vasospastic tendency is the result of degenerative changes of these vessels secondary to arterial hypertension cannot be stated from this study.

SUMMARY AND CONCLUSIONS

1. Raynaud's syndrome precipitated by cold or by work occurs in patients with arterial hypertension and with arteriosclerosis.

2. Study of a case with severe attacks revealed that the clinical manifestations were due to an irritable and vasospastic state of the small arteries and arterioles of the fingers. The venules were also in spasm during attacks.

3. Vasodilator substances, such as histamine, acetylcholine, sodium nitrite, and typhoid vaccine, failed to prevent or alter the induced attacks, even when administered in doses sufficiently large to insure their maximum systemic effect.

4. Bright red "arterial" skin color may be associated either with very rapid capillary blood flow and normal tissue metabolism, or with sudden stagnation of blood flow and unusually low tissue metabolism.

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THE CIRCULATION TIME IN VARIOUS CLINICAL CONDITIONS DETERMINED BY THE USE OF SODIUM DEHYDROCHOLATE*

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INTRODUCTION

THE velocity of blood flow or, measured inversely, the circulation time has interested investigators for the past century. A review of the earlier work and a discussion of the principles involved are found in the very comprehensive papers of Blumgart¹ and Kisch.² Accurate methods applicable to man have been evolved only in the past decade.

The blood velocity may be measured as the distance covered by a particle of blood in a fixed interval of time, or, inversely, as the time elapsing to complete a known distance. From an experimental point of view it has been simpler to measure the time rather than the distance. The methods applicable to man, with any degree of accuracy, depend upon the rapid injection of a substance in an arm vein and its detection at some distant fixed point through properties depending upon the substance's color,^{3, 4, 5} vasodilator effect,⁶ neuromuscular stimulation,^{7, 8} radioactivity,⁹ or taste.¹⁰ The time elapsing from the moment of injection to that of detection is known as the circulation time. When the method used involves primarily the blood flow through the lungs, a rough measurement of the pulmonary circulation time is obtained.

The simplest procedure was that devised by Bornstein¹¹ in 1912. He caused his patients to breathe a mixture of air with 5 to 7 per cent of carbon dioxide. As soon as the arterial blood carried the increased amount of carbon dioxide to the respiratory center, there followed an increase in the depth of respiration. The time elapsing between the start of the experiment and the onset of deeper breathing was regarded by Bornstein as half a circulation. The source of error in this method must be quite obvious when applied to patients with dyspnea, a condition in which the value of the blood velocity is of great interest.

In 1922 Koch³ injected 1.6 per cent solution of fluorescein into one cubital vein, and collected samples of blood every five seconds from the other vein. The moment of appearance of the fluorescein deter-

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mined the circulation time. The technical difficulties were the inability to detect faint traces of fluorescein, to sample the blood at second intervals and the two venipunctures. Despite these drawbacks, the general behavior of the blood circulation time in normal and pathological states was rather accurately determined by him.

A similar method but utilizing Congo-red was reported by Klein and Heineman⁴ in 1929. It suffers from very much the same objections as does the fluorescein method.

In 1922 Hirschsohn and Mandel⁷ suggested the use of calcium chloride intravenously for determining the circulation time. They injected rapidly 5 c.c. of a 10 per cent solution. A feeling of warmth and a sensation of burning in the throat indicated the arrival of the drug at the neuromuscular junction. They were particularly interested in the effect of pneumothorax upon the blood velocity through the lungs.

Kahler,⁸ using the same technic, repeated and amplified the above mentioned work in 1930. His results agree fairly well with those found by other methods. The normal values are more sharply delineated from the pathological than is possible with the dye method. Its drawbacks are the danger of slough and thrombosis from the rapid injection of calcium chloride if leakage occurs about the vein, the failure of some patients to respond, and the possibility of affecting the blood velocity itself by the use of calcium chloride.

In 1927 Blumgart and Yens⁹ introduced their radium method, and for the first time it was possible to determine the circulation time from the site of injection to the right heart and the time from this point through the lungs, to the other arm. It is the introduction of a method of measurement of the pulmonary circulation time by Blumgart and his coworker that has proved of importance. This time tends to be a constant for a particular individual in the basal state. Variations from this value occur with exercise, drugs, and in anemia, polycythemia, emphysema, congestive heart failure, myxedema and hyperthyroidism. The time bears little or no relationship to weight, height, blood pressure, or pulse rate of the individual tested. Unfortunately, the method is so technical in its execution that it is not generally applicable.

In 1928 Weiss, Robb and Blumgart¹² used the intravenous injection of 1 mg. of histamine for the determination of the blood velocity. The circulation time was that required for the appearance of a reddening of the face and a metallic taste in the mouth. The serious drawback of this method is the severity of the reaction to histamine in some patients. It is scarcely suitable for the very sick. Confirmation of their results is found in the work of Wolheim¹³ and Sebastiani.¹⁴ Winternitz, Deutsch and Brill¹⁰ found that if the histamine is diluted and a larger amount of fluid thus injected, a much shorter time is obtained in normal individuals than that found by Weiss and others. Seckel¹⁵

was able to use the histamine method in infants in whom the anterior fontanelle was still open, by injection into the longitudinal sinus through the fontanelle.

A rather complicated procedure which measured the change in volume of an extremity after the injection of an acetylcholine preparation was published in 1929 by Prusik.⁶

In a series of studies on the choloretic action of bile salts, Neubauer^{16, 17} introduced the use of sodium dehydrocholate. It is readily soluble in water and oxidizes slowly in air. Its solution has a bitter taste and is slightly alkaline. The substance was found to be practically the only bile salt that could be injected intravenously without deleterious effect. A disagreeable side action was the intensely bitter taste that followed the injection of even small amounts. Winternitz, Deutsch and Brill¹⁰ utilized this very property of the drug for the determination of the circulation time.

They injected 5 c.c. of a 20 per cent solution of sodium dehydrocholate (decholin) very rapidly (time not mentioned), and determined the moment of appearance of the bitter taste. The sensation was very transitory, lasting ten to twenty seconds, so that the test could be repeated with the needle remaining in the vein. There were no undue subjective sensations except occasional nausea. It apparently had little or no effect on the circulation itself. No alteration of the pulse rate was noted after the administration of the drug. They reported the results of over 700 injections without any complications.

It is this last method that we employed in the examination of our patients. We wish to call attention to its simplicity, and to the information which the determination of the circulation time may yield in the appropriate case.*

PROCEDURE

Although a constant amount of 5 c.c. of a 20 per cent solution of sodium dehydrocholate† was recommended by the original authors of the method, we found that an accurate response could be obtained in some patients with as little as 3 c.c. In general the faster the circulation time the less substance is needed to produce the taste. To avoid an intense reaction in patients suspected of having a very rapid time, the smaller amount may be used. In normal individuals or patients with heart disease, it is advisable to use only 5 c.c. In nearly 600 tests with 400 subjects there was always a positive response.

The test is usually performed in the morning, without breakfast, and under resting conditions. The subject lies as nearly flat in bed as possible. The arm is held at the level of the auricles. To avoid undue constriction the tourniquet is only applied just before the injection. The patient is instructed that he will experience a transient bitter taste in the mouth and tongue and is to respond at once when he perceives it. The injection is made rapidly with an 18 gauge needle

*The authors wish to acknowledge their indebtedness to Dr. Hermann Blumgart who first called their attention to this reference during a lecture on the blood velocity delivered at the Montefiore Hospital in 1931.

†The sodium dehydrocholate, known commercially as decholin sodium, was used by us.

and a 5 or 10 c.c. syringe. A stop watch records the time from the moment of injection to the arrival of the bitter taste. From 1 to 2 seconds are required for the injection. The time at the start of the injection rather than at the conclusion is taken, since the response may come with a minimum amount of the drug. The taste reaction persists for about 10 to 20 seconds. The patient's attention can be distracted from any unpleasant feeling afterwards by having him breathe deeply for half a minute. Occasionally there is a feeling of nausea shortly after the taste. In four instances, among all those tested, vomiting occurred as well. The nausea does not last more than a minute or two and is of no consequence. About 1 per cent of the patients tested also complained of pain in the right upper quadrant shortly after the injection. This may be due to sudden gall bladder distention.¹⁵ There is no danger of slough or thrombosis from paravenous infiltration. The test may be repeated as soon as desired. Most of the cases reported are the results of two or more tests on the same patient. Cooperation on the part of the patient is necessary to secure an accurate response. The test is not reliable when the subject is in stuporous condition or mentally confused or has a loss of taste in the tongue. When in doubt about the accuracy of the response, it is advisable to repeat the injection.

In a number of patients we have checked the time through the use of calcium gluconate. This substance produces a feeling of heat in the mouth and over the body similar to that caused by calcium chloride. We have found the values, by the two methods, in the same patient to be the same, within the experimental error.

The subjects studied were all at the Mount Sinai or Montefiore Hospitals or were followed from the former institution to the latter. The group with heart disease is taken almost entirely from the Montefiore Hospital, that with diseases of the thyroid gland is chiefly from the Mount Sinai Hospital and the Radiotherapy Clinic* of the Montefiore Hospital. The results from both institutions have been combined in the charts and tables.

NORMAL INDIVIDUALS

Thirty normal men and thirty normal women, chiefly of the hospital staff, were tested. Their ages ranged from nineteen to fifty-eight years. The average circulation time was 13 seconds for the group of sixty. The extremes at rest were from 10 to 16 seconds. These normal values agree closely with the results reported by Winternitz, Deutsch and Brill.¹⁰ Their upper limit of normal is set at 14 seconds, but they fail to include the time taken for the injection, which itself is usually one to two seconds. The sharpness of these normal time periods stands in contrast to the wider fluctuation found by the radium¹ and histamine¹² methods. That the results as reported by the last procedure are too high is indicated in the work of Winternitz, Deutsch and Brill previously quoted. It seems reasonable to assume that if the velocity of blood flow is not affected by the injected substance itself, the more rapid the time obtained under basal conditions, the more nearly accurate and absolute it is.

It is important to remember that exercise and excitement tend to shorten the circulation time. Under the same conditions there has

*We wish to thank Dr. M. Lenz and Dr. J. Fried for their kindness and cooperation in the study of these patients.

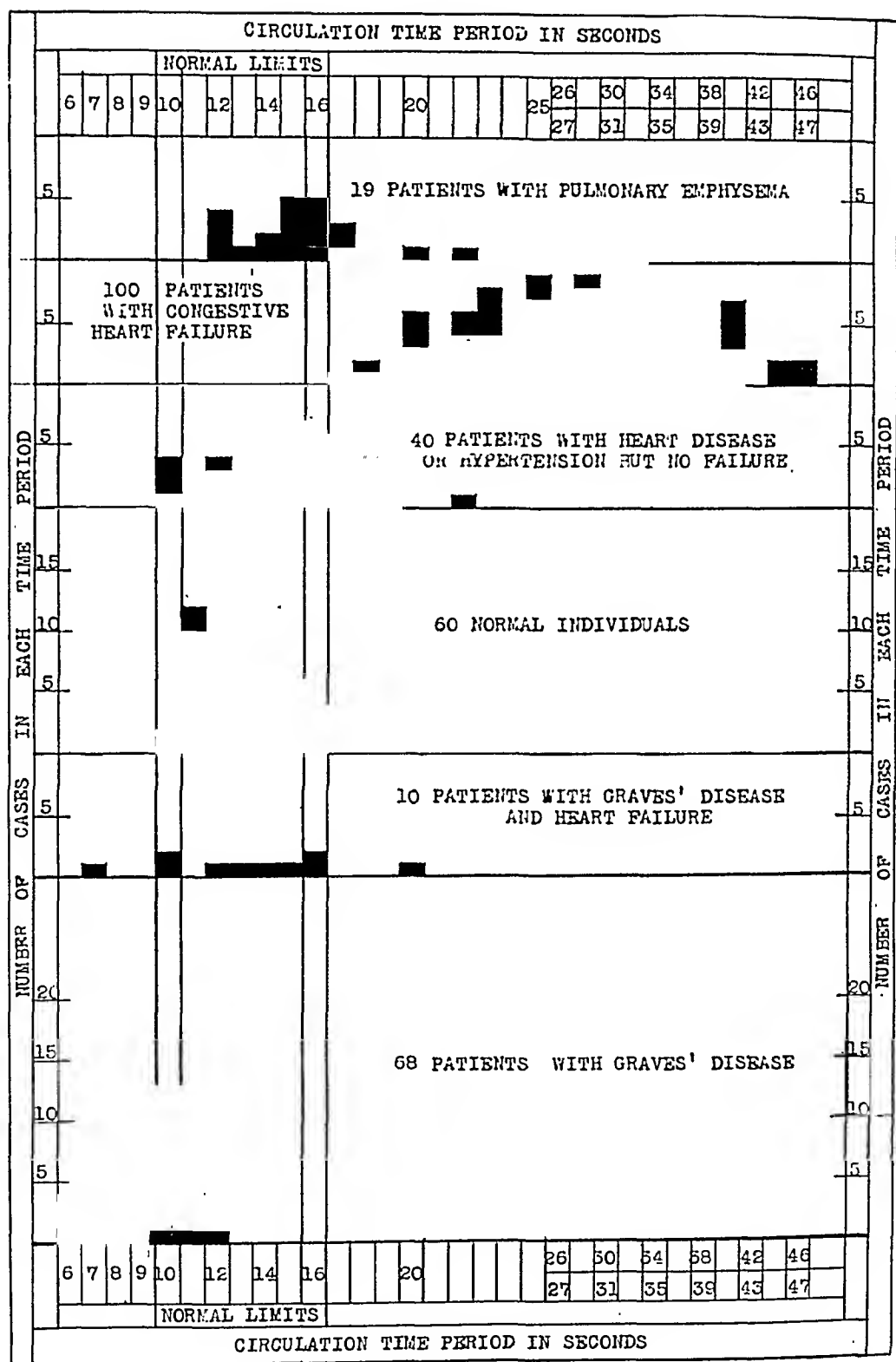


Fig. 1.—The blood circulation time in several clinical conditions.

been a remarkable agreement for the same subject. Duplicate values did not exceed 3 seconds' difference among the normal individuals.

Our data have been prepared in graphic form. Previous investigators have shown that in normal adults, the circulation time bears little or no relationship to weight, height, pulse rate and blood pressure. Our results agree with these findings. To avoid a confusion of figures, the height, weight, pulse rate and blood pressure have been omitted in the chart (Fig. 1).

HEART DISEASE

Congestive Heart Failure—Adults. Although Koch's studies³ were limited to five-second samples, he was able to prove a definite slowing of the blood stream in congestive heart failure. His observations have been confirmed by all subsequent investigators. Except in the work of Kahler⁸ and Winternitz, Deutsch and Brill¹⁰ it has not been possible to deal with absolute values since the wide range of the normal by the fluorescein, radium and histamine methods also covered a certain percentage of the prolonged values found in congestive heart failure. It is quite probable that all the last three methods yield absolute values which are too high.

In the report of Kahler⁸ it is to be noted that periods above 17 seconds are found chiefly in patients with signs or symptoms of congestive heart failure.

Winternitz, Deutsch and Brill¹⁰ set the limit of normal at 14 seconds but fail to state whether this was exclusive of the time required for injection, which itself may be 2 seconds. They likewise found prolonged time periods chiefly in patients with congestive heart failure. Blumgart¹ averaged the different groups and found the time periods of those with congestive heart failure considerably above normal.

Since there can be no sharp clinical differentiation of patients with circulatory failure from those who are just on the borderline but rather only a gradual merging of one group into another, it is to be expected that the circulation times will reflect a similar condition. In so far as it was clinically possible we have attempted to separate a group of 140 adult patients with hypertensive, arteriosclerotic, rheumatic and syphilitic heart disease into those with and those without congestive heart failure. The patients were observed for periods of time varying from weeks to months. As evidence of congestive failure in a patient with a known cardiac lesion we used the presence of (1) dyspnea, (2) pulmonary congestion on physical or x-ray examination, (3) enlargement of the liver, (4) edema, and (5) ascites. We feel justified in making the diagnosis in the presence of the first three criteria alone and at times in the presence of only the first two. In 100 patients of the 140, congestive heart failure was diagnosed. In 92 of the 100, the liver was palpably enlarged, and in 47 edema was

TABLE I
CIRCULATION TIME IN CHILDREN WITH HEART DISEASE

NAME	DATE	AGE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRES- SURE	CIRCULA- TION TIME	DIAGNOSIS AND COMMENT
<i>Group 1. Rheumatic Heart Disease Without Signs of Congestive Heart Failure</i>							
K. R. ♂	11/18/31	13	83	80	108/80	13 sec.	Chronic rheumatic cardio- valvular disease, mitral stenosis and insufficiency, chorca.
	12/ 9/31		83	100		12 sec.	Clinical condition un- changed.
P. F. ♀	12/11/31	13	95	116	80/40	13 sec.	C. R. C. V. D.,* mitral steno- sis and insufficiency, tran- sient auricular fibrilla- tion.
S. L. ♂	2/ 8/32	12.5	75	60	110/65	12 sec.	C. R. C. V. D., aortic stenosis and insufficiency.
	3/11/32		76	84		12 sec.	Condition as above.
S. C. ♂	1/ 6/32	13	100	92	130/0	17 sec.	C. R. C. V. D., aortic insuf- ficiency, mitral stenosis and insufficiency.
	2/16/32		100	78	128/0	15 sec.	Clinical condition un- changed.
F. A. ♂	12/ 9/31	12	70		128/0	10 sec.	C. R. C. V. D., aortic insuf- ficiency, mitral stenosis and insufficiency, second- ary anemia; 3,650,000 R.B.C., 70% hg.
S. H. ♂	10/ 1/32	12	64	104	120/80	11.5 sec.	C. R. C. V. D., mitral steno- sis and insufficiency.
<i>Group 2. Congestive Heart Failure in Rheumatic Fever</i>							
S. G. ♂	12/ 3/31	11	43	104	120/20	17.5 sec.	C. R. C. V. D., aortic insuf- ficiency, mitral stenosis and insufficiency, fever; liver enlarged, pulmonary congestion, pericarditis. Very apprehensive.
E. K. ♂	11/20/31	10	53	120	120/50	17 sec.	C. R. C. V. D., aortic insuf- ficiency and stenosis, peri- carditis, fever; edema present, liver enlarged. Died one week later.
<i>Group 3. Congestive Heart Failure Dominates the Clinical Picture</i>							
W. A. ♂	11/18/31	11	77	110	110/50	35 sec.	C. R. C. V. D., aortic insuf- ficiency, mitral stenosis and insufficiency; liver en- larged, edema of lower extremities present.
	11/20/31		77.5	100		29 sec.	Clinical condition un- changed.
	12/ 8/31		72	100	108/50	28 sec.	Lost 5 pounds of edema fluid after salyrgan in- jection; condition other- wise the same.
S. T. ♂	11/18/31	11	78	84	90/60	38 sec.	C. R. C. V. D., mitral steno- sis and insufficiency, auricular fibrillation, liver enlarged, edema present.

TABLE I—CONT'D

NAME	DATE	AGE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRES- SURE	CIRCULA- TION TIME	DIAGNOSIS AND COMMENT
<i>Group 3—Cont'd</i>							
S. T. ♂	12/ 9/31		70	80	92/60	23 sec.	Has lost 8 pounds of edema fluid on salyrgan and digitalis therapy; much improved; liver edge still at previous level, no edema.
	1/ 6/32		70	80		24 sec.	Clinical condition as noted on 12/9/31.
N. R. ♀	12/11/31	13	84	118	124/0	23 sec.	C. R. C. V. D., aortic insufficiency; liver enlarged.
	1/12/32		85	105		21 sec.	Clinical condition unchanged.
I. K. ♀	12/11/31	11	59	120	80/40	24 sec.	C. R. C. V. D., mitral stenosis and insufficiency; liver enlarged.
	1/12/32		62	100		21 sec.	Clinical condition unchanged.
R. L. ♀	12/16/31	14	120	84	110/30	40 sec.	C. R. C. V. D., mitral stenosis and insufficiency, auricular fibrillation; liver enlarged, edema present.
	1/ 6/32		111	80		45 sec.	Has lost 9 pounds of edema fluid; improved clinically.
R. T. ♀	3/ 2/32	15	58.5	100-120	90/60	25 sec.	C. R. C. V. D., mitral stenosis and insufficiency, acute pleurisy; liver enlarged; temperature 101.8°.
	4/ 4/32		62	180	95/65	27.5 sec.	Onset of paroxysmal tachycardia that lasted 1½ hours at time of circulation test. Only complaint was palpitation.
	5/ 6/32			110	92/60	25 sec.	Feels better than on admission; liver still enlarged.
	10/20/32			90	100/60	30 sec.	Auricular fibrillation has lasted for 10 days, rapid ventricular rate at start—154 per minute, now controlled by digitalis. Clinically patient feels worse; congestive heart failure present.
	10/25/32			87	110/65	28 sec.	Regular rhythm restored following quinidine; clinically improved; congestive heart failure still present.
<i>Group 4. Borderline Congestive Heart Failure and Rheumatic Fever</i>							
J. P. ♂	12/ 9/31	12	57	120	110/68	16 sec.	C. R. C. V. D., mitral stenosis and insufficiency. On borderline of congestive failure.
	2/ 5/32		59.5	100		19.5 sec.	Clinical condition somewhat worse than on admission; liver edge just palpable.

TABLE I—CONT'D

NAME	DATE	AGE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRES- SURE	CIRCULA- TION TIME	DIAGNOSIS AND COMMENT
<i>Group 4—Cont'd</i>							
	5/ 6/32		58	112	102/60	14 sec.	Respiratory infection, cough- ing. Liver edge 2 fingers below costal border.
	6/29/32		64	104		14 sec.	Clinical condition good; liver not palpable.
	10/ 1/32		66	104	105/60	15 sec.	No fever; clinical condition good; liver edge barely palpable.

*C. R. C. V. D. — Chronic rheumatic cardiovalvular disease.

present. The other 40, although suffering from complaints referable to the cardiovascular system could not be considered as belonging to the first group. Their complaints were either precordial pain, dyspnea, or weakness without accompanying signs of pulmonary or hepatic congestion or edema of cardiac origin.

Every one of the 100 patients with clinical congestive heart failure had a circulation time that was more than 17 seconds. In 96 of the 100 the time was 20 seconds or more and ranged up to 47 seconds. The other group of 40 without congestive failure contained all grades from those who barely showed any cardiac involvement to those who were on the verge of failure. Yet of this group, in only 10 was the circulation time 17 seconds or more. Nine of these 10 periods were between 17 and 19 seconds and the tenth one was 21 seconds. The general average of the group without congestive failure is about 2 seconds higher than normal. The general average of the group with congestive failure was 26 seconds, or 13 seconds above the normal average.

Congestive Heart Failure—Children. The blood velocity of 15 children with chronic rheumatic cardiovalvular disease was investigated. Their ages ranged from ten to fourteen years. Technical difficulties and the possibility of an inaccurate response precluded the use of younger children. Between 3 and 5 c.c. of sodium dehydrocholate were injected, depending upon the age and clinical condition of the patient (Table I).

In 6 of the 15 children there was no evidence of congestive heart failure. Clinically they suffered more from the effects of rheumatic fever than from a failing circulation. As the table indicates, undoubted valvular lesion was present in each one. The average circulation time for this group was 13 seconds, with the extremes at 12 and 17 seconds. We have had no opportunity of determining the circulation time in normal children and but little data are available in the literature. In two patients, eight and eleven years of age admitted for surgical treatment without any cardiac complications, the circu-

lation time was 10 seconds in each. We believe that the circulation should not be much different from that in adults.

In two of the 15 children congestive heart failure occurred during the course of a severe rheumatic pancarditis. The patients were critically ill, and one died several days after the test was performed. The circulation time was 17 seconds in each case. The enlargement of the liver and the signs of pulmonary congestion lead one to assume a fairly severe grade of cardiac failure. The time of 17 seconds appears rather short and may be the result of the active rheumatic fever.

In six of the children the signs and symptoms of congestive heart failure outweighed the manifestations of the rheumatic activity. The circulation time for this group was from 21 to 45 seconds. Although the number of cases is small, they would appear to behave very similar to the adult group.

One patient, J. P. (Table I), was on the borderline of congestive heart failure clinically. His circulation time fluctuated on five occasions from 14 to 19.5 seconds. As the table indicates, the shortest time was obtained during the course of a respiratory infection. There was no elevation in temperature accompanying it.

Miscellaneous Cardiac Conditions—Congenital heart disease. One patient with a congenital heart lesion, diagnosed as a stenosis of the pulmonary artery and an overriding aorta, had on three occasions circulation time periods of 11, 7.5 and 9.5 seconds. There were marked cyanosis and dyspnea present but there was no evidence of congestive heart failure. The rapid time of 7.5 seconds is suggestive of a venous arterial shunt in the heart, whereby a part of the circulating blood is pumped directly to the tongue without passing through the lungs.

Subacute Bacterial Endocarditis. Of four patients with subacute bacterial endocarditis engrafted upon rheumatic valvular disease, two showed normal circulation time periods. One, with a marked secondary anemia and elevated temperature had a time of 9 seconds. The fourth case had a circulation time of 27 seconds and presented undoubted clinical evidence of congestive heart failure and auricular fibrillation. Despite the severity of the pathological process in the heart, circulation time periods within normal limits were found in those patients who showed no evidence of congestive heart failure.

Pericardial Tumor. One patient with a pericardial tumor which invaded the auricle and clinically led to congestive heart failure had a circulation time of 20.5 seconds, in keeping with what was expected. The diagnosis was confirmed at the post-mortem examination.

Cardiac Asthma. We were able to determine the blood velocity in two patients during attacks of paroxysmal cardiac dyspnea that simulated bronchial asthma. Both patients suffered from arteriosclerotic heart disease and had evidence of mild congestive heart failure. The circu-

TABLE II

VARIATIONS IN THE CIRCULATION TIME WITH CHANGES IN THE CLINICAL CONDITION OF THE PATIENT

NAME AGE SEX	DATE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRESSURE	CIRCULATION TIME	DIAGNOSIS AND COMMENT
E. W. 52 years ♀	11/27/31	93	100	140/100	38 sec.	Hypertension and coronary artery disease. Bundle-branch block. Edema and ascites present.
	1/ 6/32	111	84	130/90	54 sec.	Has gained 18 pounds of edema fluid; clinically much worse.
	2/ 5/32	109	86	135/90	43 sec.	Edema and ascites still present.
	3/18/32	109	88	145/96	48 sec.	Edema and ascites still present.
	5/11/32	109	100		45 sec.	Edema and ascites still present.
H. R. 57 years ♂	11/18/31	135	76	110/70	27 sec.	Coronary artery disease. Auricular fibrillation. Edema and ascites present.
	11/25/31	126	70		33 sec.	Slight improvement due to loss of 9 pounds of edema fluid with digitalis and salyrgan.
	12/ 2/31	120	84	106/68	33 sec.	Continues to lose edema fluid; no ascites present.
	12/15/31	123.5	90		25 sec.	Very much improved; no edema present.
	1/ 7/32	127	92	112/70	35 sec.	Still in congestive heart failure, but no edema or ascites.
A. G. 71 years ♂	11/20/31	125	92	96/75	43 sec.	Hypertension, coronary artery disease, auricular fibrillation. Edema, ascites, hydrothorax.
	12/16/31	114	70		28 sec.	Loss of 11 pounds of edema fluid. Ascites and hydrothorax cleared up.
	12/18/31	115	80	110/80	26 sec.	Continues to improve clinically. Edema absent.
	1/27/32	122	84		25 sec.	State of nutrition better. Edema absent.
	2/ 8/32	125	90	100/70	26 sec.	State of nutrition better. Edema absent. Liver still enlarged.
	3/21/32	119	72		32 sec.	Returned in congestive failure after leaving the hospital. Edema, ascites present.
A. B. 54 years ♀	12/ 2/31	120	88	182/100	16 sec.	Hypertensive heart disease, pulmonary congestion. Liver edge barely palpable.
	12/16/31	123	84	185/100	18 sec.	Has gained 3 pounds of edema fluid. Congestive failure more pronounced.
	12/21/31	121	112	180/90	22 sec.	Respiratory infection; fluids forced; liver edge now 2 fingers below the costal border; temperature 100°.

TABLE II—CONT'D

NAME AGE SEX	DATE	WEIGHT IN POUNDS	PULSE RATE	BLOOD PRESSURE	CIRCULATION TIME	DIAGNOSIS AND COMMENT
C. T. 56 years ♂	11/25/31	110	42	230/60-80	25 sec.	Coronary artery disease, complete heart-block, congestive heart failure with edema.
	1/ 6/32	107	46	210/80	35 sec.	General condition worse; edema of lower extremities pronounced.
	2/ 8/32	107	36	220/90	34 sec.	Condition the same for past month.
	3/ 2/32	104	34	204/84	35 sec.	Slight change in physical status.
	5/ 6/32	107	72	160/70	20 sec.	Spontaneous restoration to sinus rhythm. Subjectively and objectively very little change.
	5/ 8/32	106	38	180/80	37 sec.	Reversion to heart-block after 3 days; feels worse; no changes objectively.

TABLE III

CIRCULATION TIME IN POLYCYTHEMIA

NAME	AGE	TOTAL RED BLOOD COUNT	HEMO- GLOBIN	TOTAL BLOOD VOLUME	VOLUME PER KILOGRAM	CIRCULATION TIME	BLOOD PRES- SURE	DIAGNOSIS
A. M. ♂	50	6,250,000	120%	5,220 c.c.	87 c.c.	16.5 sec.	130/80	Secondary polycythemia. Duodenal ulcer.
J. C. ♂	28	7,600,000	125%	6,190 c.c.	113 c.c.	16.5 sec.	106/76	Polycythemia vera.
J. A. ♀	34	9,350,000	154%	3,300 c.c.	193 c.c.	18.5 sec.	126/88	Polycythemia vera.
S. D. ♀	56	8,500,000	137%	6,900 c.c.	133 c.c.	18 sec.	184/96	Polycythemia hypertonica.

lation time periods were found prolonged but not radically different from the time periods between the episodes of dyspnea.

Tachycardia and Bradycardia. In two patients we had the opportunity of determining the effect of marked fluctuation in the pulse rate on the circulation time. One was a child, R. T. (Table I), who had chronic rheumatic cardiovalvular disease with congestive failure. She was subject to attacks of paroxysmal tachycardia (demonstrated by the electrocardiogram). Her complaint at such times was chiefly cardiac palpitation. The episode began and ended suddenly and lasted from several minutes to several hours. As the table shows, the circulation time remained practically the same during an attack that lasted one and one-half hours in which the usual rate of 100 to 120 had risen to 180 beats per minute.

The other patient, C. T. (Table II), suffered from arteriosclerotic heart disease with complete heart-block. His past history showed that on several occasions he had established a regular sinus rhythm with a pulse rate up to 84 per minute, instead of his usual rate of 38 to 46 per minute during block. Such changes were spontaneous, lasted several days, and were not accompanied by subjective or objective improvement in the clinical condition. The patient's basic circulation time during the four months prior to his latest episode of sinus rhythm was 35, 34, and 35 seconds, with his rate fluctuating from 34 to 46 per minute. Examined on the third day of a period of sinus rhythm with a rate of 72, the circulation time was found to be 20 seconds. Two days later the rate was 38 and the circulation time had returned to its previous level—37 seconds. For five days the patient had had a sinus rhythm, demonstrated by numerous electrocardiographic tracings. There had been little or no change objectively or subjectively in his clinical condition. Congestive failure continued as before; yet the velocity of blood flow had almost doubled. Significant as well is the drop in blood pressure that occurred at the same time (see Table II).

Comment. With the exception of one patient with heart-block, described in Table II, no constant relationship was found between the blood pressure, venous pressure, pulse rates, or weight of the patient and the circulation time. While there is a tendency for the time to be prolonged in proportion to the degree of congestive heart failure, there were exceptions to this as well, especially in the presence of active rheumatic fever. As improvement occurred with digitalis and diuretic therapy, the time was generally shortened. In those who improved sufficiently as no longer to be classified in congestive failure, the time tended to return to the upper limit of normal. However, the correlation was not so exact as to make the test of prognostic value.

Nearly all those who showed prolonged times were tested twice. Whereas in the normal the duplicate tests under the same conditions showed a maximum difference of plus or minus 3 seconds, those with prolonged time showed fluctuations up to 8 seconds, especially in the group with periods above 30 seconds. Similarly, the deviation from the general average of 13 seconds in the normal was plus or minus 3 seconds, whereas in the group with congestive heart failure it was minus 9 seconds to plus 24 seconds. It was rather a surprising clinical demonstration in many cases to obtain repeated circulation times in the same patient agreeing to one second.

DISEASES INVOLVING THE LUNGS AND PLEURA

Pulmonary Emphysema. The difficulty of accurately diagnosing cardiac failure in the presence of pulmonary emphysema is well recognized clinically. The cardinal symptoms of dyspnea, cyanosis and cough are present in both conditions.

Blumgart and Weiss¹⁹ found the circulation time in 21 out of 25 patients with pulmonary emphysema to be within normal limits. "The normal or even increased velocity of blood flow particularly in those patients who had many of the symptoms and signs of severe circulatory failure such as conspicuous weakness, cyanosis and dyspnea is of great importance. It shows that pulmonary emphysema alone is sufficient for the production of these symptoms and signs." (Blumgart.)

Of a total of 19 patients with pulmonary emphysema either idiopathic in origin or secondary to a long-standing asthma, bronchitis or fibroid tuberculosis, normal circulation time periods were found in 13 patients. In one of these there was clinical evidence of congestive heart failure. In the remaining six patients there was a slight prolongation of the circulation time—up to 22 seconds. In four of these six patients there was clinical evidence of congestive heart failure, either secondary to right heart involvement or upon an independent basis.

Pneumonia, Tuberculosis. Hirshsohn and Mandel,⁷ using calcium chloride, showed that the blood velocity in pulmonary tuberculosis is within normal limits and is not affected by the volume of the lung. Pneumothorax, apparently, has little effect upon the velocity of the circulation through the lung. We examined a group of 9 patients with pulmonary disease in whom we were certain that no cardiac complications existed. Four of these patients had at the time a lobar or bronchopneumonia accompanied by elevation in pulse, temperature and respiratory rates. The other five patients suffered from active pulmonary tuberculosis.* The circulation time period for the group ranged from 7.5 to 13.5 seconds and the average time was 11.2 seconds.

In two patients with pulmonary tuberculosis in whom evidence of congestive heart failure was found during life and at necropsy, the circulation time was beyond 20 seconds.

In the presence of the increased metabolic rate accompanying fever it seems reasonable to expect an increased blood velocity. The general average for the group is nearly 2 seconds faster than normal. In evaluating congestive heart failure in such a group it would be safe to accept time periods between 16 and 20 seconds as suspicious of cardiac involvement.

POLYCYTHEMIA AND MYXEDEMA

The only other conditions that may produce a slowing of the blood velocity or a prolongation of the circulation time are polycythemia¹ and myxedema.¹ In six patients with polycythemia observed by us the time was prolonged. In two of these there was undoubted evi-

*These five patients were seen through the courtesy of Dr. Maurice Fishberg on the Tuberculosis Division.

dence of severe coronary artery disease, so that it was not possible to place the responsibility upon the polycythemia alone. In the other four there was no evidence of cardiac failure. The relationship of the polycythemia to the circulation time in the other four patients is shown in Table III. The time periods begin at the upper limit of normal and run to 18.5 seconds. The prolongation is not very striking; yet it is in keeping with the altered physiology of the blood movement in polycythemia.

One patient with myxedema was observed before treatment. Her basal metabolic rate was minus 32 per cent, pulse 70, hemoglobin 70 per cent, red blood count 3,700,000, and the circulation time 21 seconds. After the administration of 44 grains of thyroid, the patient showed evidence of overdosage. Excitement was present, the temperature was elevated to 100.4° F., pulse was 84 per minute, the basal metabolic rate was minus 10 per cent, and the circulation time 8 seconds. Another patient had a circulation time of 16.5 seconds with a basal metabolic rate of minus 36 per cent. Following thyroid therapy, the basal metabolic rate rose to minus 6 per cent and the circulation time decreased to 13 seconds.

GRAVES' DISEASE

Blumgart, Gargill and Gilligan²⁰ were the first to measure the blood velocity in patients with thyrotoxicosis. In 13 patients they found an increased speed of blood flow through the lungs that was 85 per cent faster than the average normal. They were able to relate the rapid time to the elevation in the basal metabolism. It appeared to be an almost linear function of the latter. With a reduction in basal metabolic rate to normal the circulation time approached the normal.

Kahler⁸ reported the results of 6 tests on the same number of patients. The times ranged from 7 to 12 seconds; the average of the group was definitely faster than the normal.

We were able to perform 100 tests of the blood velocity on 78 patients who suffered from Graves' disease and in whom the basal metabolic rate was elevated from plus 5 per cent to plus 87 per cent. Of these 78 patients, 10 had at the time of measurement evidence of cardiac failure, as a possible result either of the thyrotoxicosis, or of a coincidental cardiac lesion. The average circulation time for the group of 68 without cardiac failure was 9 seconds in contrast to the normal of 13 seconds. The individual times ranged from 6.5 to 12 seconds. The circulation times of the patients with cardiac failure ranged from 6.5 to 19 seconds and averaged 13 seconds. These times bear out the findings of Blumgart, Gargill and Gilligan.¹⁹ For the degree of cardiac failure present one would have expected a much more prolonged time for the group, at least 20 seconds. The circula-

tion time period in patients with congestive heart failure and Graves' disease seems to be an arithmetical average of what would be expected in either condition alone. Through the measurement of the circulation time it was possible to recognize two cases of Graves' disease which at first impression had been clinically masked by symptoms of a coincidental rheumatic heart disease.

In four patients with enlargement of the thyroid gland due to adenomata and not associated with evidence of hyperthyroidism, the circulation time periods were 10.5, 12, 12, and 14 seconds.

In four patients with neurocirculatory asthenia whose complaints were very similar to those of patients with hyperthyroidism, but whose basal metabolic rates were normal, the circulation time periods were from 10 to 12.5 seconds. Further studies in this group are contemplated. No conclusion can be drawn from so small a number of cases.

An attempt to relate the circulation time to the elevation in the pulse rate in the patients with Graves' disease was not successful. Neither have we been able to relate as closely as Blumgart did, the increased blood velocity to the elevation in the basal metabolic rate. In general we found that those with the highest basal metabolic rate and the fastest pulse rate had the shorter times, but, likewise, times of 8 seconds were found in patients whose metabolic rate was only 16 per cent above normal and who clinically had active Graves' disease. In the performance of the test on patients with hyperthyroidism complete cooperation is absolutely essential for an accurate result. Unless the test is done with the patient completely at rest, a shorter time than is normal for that patient will be obtained. Blumgart has pointed out that in addition the variable factor of arm to heart time may be responsible for the failure to correlate the data.¹

ANEMIA

The consensus of opinion regarding the dynamics of the circulation in severe anemia is that the cardiac output per minute tends to increase and the velocity of blood flow with it. Such a mechanism is one of the means of supplying the requisite amount of oxygen to the tissues when a deficiency of hemoglobin exists. The other mechanism is more complete utilization of the arterial supply of oxygen with a resultant greater arteriovenous oxygen difference.

In a study of 18 patients with severe anemia, both primary and secondary, in none of whom symptoms of cardiac failure existed so far as could be determined clinically, the average circulation time was 12 seconds. The individual values fluctuated from 9 to 15 seconds. The average in our series of 60 normal controls was 13 seconds, with fluctuations from 10 to 16 seconds. The difference is not very striking, but no conclusions can be drawn from so small a group.

MISCELLANEOUS CLINICAL CONDITIONS

It was of interest to investigate the circulation time in a group of diseases in which enlargement of the liver, edema, ascites, or dyspnea might raise the question of circulatory failure in the differential diagnosis. Such conditions are chronic glomerulonephritis, the nephroses, cirrhosis of the liver, the obscure group of hepatosplenomegalies, and occasionally neoplasms.

Cirrhosis of the Liver. In 9 patients with hepatic enlargement due to cirrhosis, amyloidosis, or hemochromatosis, despite the occasional presence of marked ascites, the circulation time was normal. In 2 patients with a hepatosplenomegaly of unknown etiology and normal blood findings, the circulation time was likewise normal.

Carcinoma and Sarcoma. In 16 patients with carcinoma or sarcoma involving different abdominal organs and accompanied in some by secondary anemia, the circulation time was 10 to 15 seconds.

Nephritis. In glomerulonephritis the blood velocity was investigated by Koch³ and Kahler⁵ and found to be more rapid than normal. This is due to the secondary anemia usually seen in those patients. We examined 13 patients whose clinical picture was primarily renal in origin.

In 5 patients with chronic glomerulonephritis with and without edema, the circulation time was 11 to 14 seconds. There was no evidence of congestive heart failure in any of the five. Moderate to severe anemia, hypertension, cardiac hypertrophy and dilatation were present in all.

In 4 patients with renal insufficiency, either due to glomerulonephritis or arteriosclerosis and complicated by congestive heart failure, the circulation time was prolonged beyond 20 seconds in two and at 16 and 17 seconds in the other two patients. There was a severe secondary anemia present in all of them. Those with times above 20 seconds died within a short time after the test. At autopsy there was confirmation of the congestive failure. Whether the time in any individual patient is prolonged beyond 20 seconds depends upon the degree of heart failure and the admixture of anemia.

Normal circulation times were found in one patient with marked hypertension and renal insufficiency due to uric acid calculi, in two patients with amyloid nephrosis, and in one with a combination of diabetes mellitus, nutritional edema and renal insufficiency due to calculi.

EFFECT OF EXERCISE AND NONBASAL STATES

Strictly basal conditions such as twelve hours fasting and one hour absolute rest were only adhered to in about 50 per cent of our cases investigated. We were more interested in securing the usual value with the subject at rest. The slight difference that occurs between

the strictly basal and the resting states we found to fall within the limit of the experimental error. In patients with congestive heart failure Kahler⁸ found that even moderate exercise did not affect the circulation time materially. These patients are already working with their maximal cardiac reserve. They are unable to meet the demands for increased work on the part of the circulation.

In five normal subjects who were examined by us during a period of moderate activity, such as routine floor nursing, the circulation time was found to be at the faster level of normal in three. In the two others the time periods were as rapid as 8 seconds. Kahler⁸ reported shortening of the circulation time from 1 to 4 seconds in normal individuals after moderate exercise.

The importance of maintaining basal conditions is indicated in the patients suspected of Graves' disease. The circulation time of an apprehensive, nervous patient without hyperthyroidism may be as rapid as one with a markedly elevated basal metabolic rate.

DISCUSSION

The condition of greatest clinical importance in which a slowing of the blood stream occurs is congestive heart failure. Here it is independent of the etiological factor, whether rheumatism, hypertension, arteriosclerosis, or syphilis. Auricular fibrillation, when present, influenced the circulation time in our cases only in so far as it was associated with congestive heart failure. The significance of a prolonged circulation time from a teleological point of view is beyond the scope of this communication. Clinically, it is of importance in the differential diagnosis of cardiac failure from conditions simulating it. Excepting one case with heart failure in the course of pulmonary emphysema, a prolonged circulation time was found in every patient with edema of cardiac origin. Conversely, a normal time in the presence of undoubted clinical cardiac failure should make one search for factors which would tend to increase the velocity of blood flow. The most usual are hyperthyroidism, fever and severe anemia. Similarly, in clinical hyperthyroidism a normal or prolonged circulation time should lend suspicion to early cardiac failure.

In 92 per cent of our patients with congestive heart failure enlargement of the liver was present on palpation. In all these the circulation time was prolonged beyond normal limits. Conversely, enlargement of the liver accompanied by a normal circulation time in heart disease has led us to investigate for a possible hyperthyroidism, or an independent cause for the liver enlargement. In two of our patients with hypertension and enlarged liver, congestive heart failure was suspected because of the large liver. A normal circulation time led to a more careful review of the history and revealed a cirrhosis of the liver as the responsible factor for the hepatic enlargement.

The recognition of cardiac failure in the presence of one or two other clinical conditions such as nephritis, amyloid nephrosis, tuberculosis, cirrhosis of the liver, and starvation edema is sometimes a difficult clinical problem. If the failure has progressed to a degree responsible for liver enlargement or edema, the circulation time will be found prolonged.

In congestive heart failure accompanying or caused by pulmonary emphysema a comparatively slight diminution of the blood velocity was noted by Blumgart.¹ Our patients showed similar findings. No satisfactory explanation for this phenomenon can be offered at present.

SUMMARY

1. The several methods proposed for the determination of the velocity of blood flow or circulation time and the results obtained are reviewed.

2. A simple procedure utilizing the injection of sodium dehydrocholate (decholin-sodium) is outlined for performing the test. The precautions to be observed are discussed.

3. The average circulation time in normal resting adults for the blood to travel from the arm vein, through the heart and lungs, and up to the mouth, is 13 seconds, as determined by sodium dehydrocholate. The normal range is 10 to 16 seconds.

4. The blood velocity was determined in 140 adult patients with heart disease due either to hypertension, arteriosclerosis, rheumatic fever, or syphilis. In so far as it was possible clinically, they were divided into two groups: those without and those with manifestations of congestive heart failure.

(a) There were 40 patients in the group without cardiac failure. The circulation time in 30 of these was within normal limits. In the remaining 10 patients the time was between 17 and 21 seconds. The general average for the group was 15 seconds, only 2 seconds above the average for normal adults.

(b) There were 100 patients in the group with signs of congestive heart failure. In 96 of these 100 patients the circulation time was 20 seconds or more and ranged up to 47 seconds. In only 4 of the patients was the circulation time less than 20 seconds. It was not less than 17 seconds in any of the four. The general average for the group was 26 seconds—twice the average for normal adults.

5. The blood velocity of a group of 15 children with rheumatic heart disease was investigated. Their general behavior was similar to that of adults. Active rheumatic fever tended to increase the blood velocity in two of these children in whom congestive heart failure was also present.

6. The blood velocity was determined in patients with such different cardiac conditions as congenital heart disease, subacute bacterial endo-

carditis, paroxysmal cardiac dyspnea, pericardial tumor, paroxysmal tachycardia, and heart-block. Its significance in these conditions is discussed.

7. Caution must be exercised in interpreting the values for the circulation time in patients suspected of having heart failure in the presence of pulmonary emphysema or marked pulmonary fibrosis.

8. Fever and anemia tend to increase the velocity of blood flow.

9. A slowing of the blood velocity was found in patients suffering from polycythemia or myxedema.

10. The blood velocity was determined in 78 patients with clinical manifestations of Graves' disease. They were divided into two groups: those without and those with evidence of heart failure.

(a) In 68 patients who showed no evidence of heart failure the blood velocity was distinctly faster than normal. The average for the group was 9 seconds and the extremes ranged from 6.5 to 12 seconds.

(b) In 10 patients with signs of cardiac failure in addition to the Graves' disease, the circulation time tended to be an arithmetic average of the two conditions. The average for the group was 13 seconds.

11. Through determination of the blood velocity, the possibility of recognizing congestive heart failure in the presence of such different clinical entities as cirrhosis of the liver, carcinoma, Bright's disease, and hyperthyroidism is indicated.

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CONGENITAL ANOMALIES OF THE CORONARY ARTERIES:
REPORT OF AN UNUSUAL CASE ASSOCIATED WITH
CARDIAC HYPERTROPHY*

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DEVELOPMENTAL defects of the coronary arteries unassociated with co-existing congenital anomalies of the heart or great vessels are of interest because of their infrequent occurrence and the possibility of their serious significance.

In 6,800 post-mortem examinations during the past 37 years at the Massachusetts General Hospital anomalies of the coronary arteries of sufficient extent to warrant mention in the anatomical diagnosis of the cases have been noted in only 4 instances. Except in the case herewith recorded, the remaining abnormalities were incidental post-mortem findings of no clinical importance in three adult male patients; one consisted of a small accessory right coronary artery, the second comprised a single normal-sized coronary artery, the left, which gave rise shortly after its origin to a branch which followed the course usually taken by the absent right coronary artery, and in a third instance the right coronary was much smaller than normal with its circumflex branch extending only 2 cm. from its origin, whereas the size and distribution of the circumflex branch of the left coronary artery in contrast were considerably larger than normal.

Significant abnormalities of origin where one of the major coronaries arises from the pulmonary artery are important in that extensive degenerative changes in the myocardium may result from the inadequate blood supplied to the region involved; or, if the patient survives to adult life, which is exceptional, curious dilated and tortuous arterio-venous aneurysms may develop upon the heart wall. We are reporting a case recently encountered at the Massachusetts General Hospital which presented the rare combination of a left coronary artery of normal size arising from the pulmonary cone co-existent with an otherwise unexplained hypertrophy of the heart as a whole, together with degenerative changes in the wall of the ventricle largely confined to the area supplied by this malposed vessel.

*From the Cardiac Clinic of the Massachusetts General Hospital, Boston, Mass.
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We have encountered in the literature only eight cases where one or other of the main coronary arteries, usually the left, arose from the pulmonary artery, and a few additional cases in which an accessory third coronary had a similar origin. A review of the reported cases reveals features of unusual interest which will be commented upon later.

CASE REPORT

A three-months-old male infant weighing 11 pounds was admitted to the hospital on July 26, 1932, because of recurring attacks of dyspnea, pallor, and profuse sweating for the preceding two weeks. Delivery had been entirely normal and at term. Both parents as well as an older brother two years of age are normal.

Nothing remarkable was noted about the patient until the tenth week; while nursing from the bottle the onset of an unusual group of symptoms occurred which

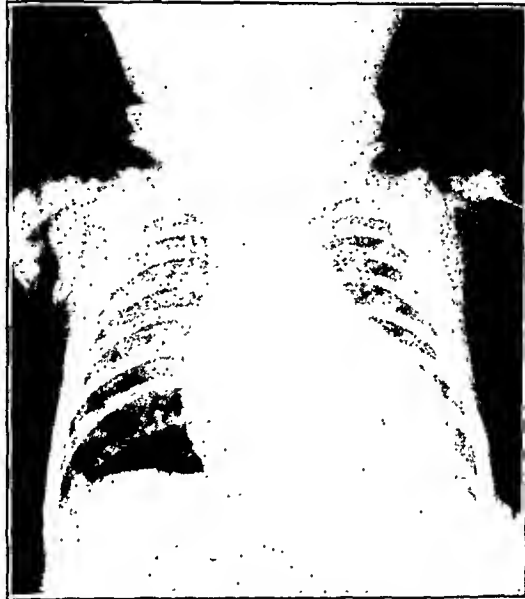


Fig. 1.—An x-ray film of the chest showing the diffuse cardiac enlargement which was most prominent in the region of the ventricles. The tube distance in this instance was seven feet from the heart.

consisted of paroxysmal attacks of acute discomfort precipitated by the exertion of nursing. The infant appeared at first to be in obvious distress as indicated by short inspiratory grunts, followed immediately by marked pallor and cold sweat with the general appearance of severe shock. Occasionally with unusually severe attacks there appeared to be a transient loss of consciousness. The eructation of gas at times seemed to relieve the discomfort and to shorten the duration of an attack, which usually lasted from five to ten minutes, and following which the infant might proceed to nurse without difficulty and remain free of symptoms for several days. It is noteworthy that during the above seizures cyanosis was not an outstanding sign, but appeared only when the infant cried vigorously, and even then was not pronounced. The lungs remained free of congestion and there was no significant change in the rate or rhythm of the heart. Convulsions never occurred even during the transient periods of apparent unconsciousness. These observations were first made by the infant's father who is himself a physician and a very careful observer, and were confirmed by one of us.

The attacks increased in severity and the child was admitted to the hospital for study. X-ray films of the chest taken before hospitalization revealed diffuse cardiac enlargement chiefly in the region of the ventricles. This finding was confirmed by films taken after admission (Fig. 1). In the hospital the child appeared to be essentially a normal infant, and the only abnormal finding on physical examination was a definite increase in the area of cardiac dullness. No murmurs were audible, and no clubbing of the fingers or constant cyanosis was noted. The electrocardiogram showed normal axis deviation, but well marked inversion of the T-waves in all leads, of the coronary type (late inversion) (Fig. 2). We considered this change in the T-wave significant especially in that no digitalis or other drug had been administered. Low voltage of the QRS complexes was also present.

During observation in the hospital the child appeared to be doing well. Slight pallor was present at times after nursing or crying. On August 9, 1932, he had a severe attack of difficult respiration with expiratory grunts and for the first time

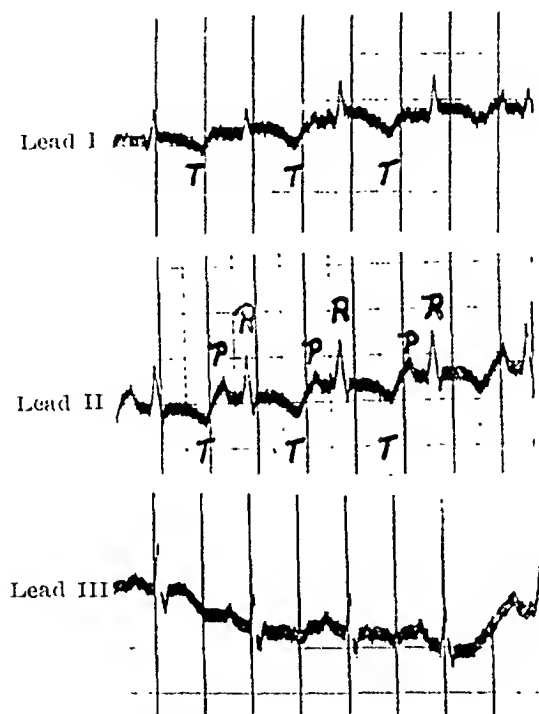


Fig. 2.—An electrocardiogram showing a late and deep inversion of the T-wave of the coronary type especially well shown in Leads I and II. Time interval is 0.2 second.

marked cyanosis. He was placed in an oxygen tent without significant improvement. Death occurred eighteen hours later apparently from respiratory failure. The clinical diagnosis was congenital idiopathic hypertrophy of the heart.

Necropsy.—A post-mortem examination performed twelve hours after death revealed the following findings: The thymus was normal. The liver extended 6 cm. below the xiphoid and 4 cm. below the costal margin. It weighed 185 grams (normal 140 grams). The kidneys were normal. The left lung was moderately collapsed as a result of pressure from the enlarged heart.

The heart weighed 91 grams (normal 25 grams). The left ventricular wall measured 11 mm. and the right 3 mm. in thickness. The chamber of the left ventricle (Fig. 3) was large and its wall occupied the entire apex of the heart, whereas the right ventricle (Fig. 4) was relatively smaller than normal with its tip 2 cm. from the apex. All of the valves were normal—thin and sufficient—with circumferences as follows: mitral 4.4 cm., aortic 2.4 cm., tricuspid 5.0 cm., and the

pulmonic 2.3 cm. The right coronary artery (Figs. 3 and 5) arose at its usual site from the aorta by one large mouth and an adjacent small mouth, the latter supplying branches to the upper portion of the right ventricle. The larger mouth communicated with a normal-sized right coronary which coursed along the auriculo-ventricular groove giving off anterior branches to the right ventricle and a large posterior descending branch which occupied the posterior sulcus between the right and left ventricles and continued almost to the apex (Fig. 5). The main right coronary artery continued in a horizontal direction to a point where the inferior vena cava entered the right auricle, and in this region bent downward to fade out over the wall of the left ventricle posteriorly. The left coronary artery, normal in size, arose from the pulmonary artery (Figs. 4 and 5). A few millimeters from its mouth it divided in a Y-shaped fashion. The larger branch coursed downward over the apex, then curved backward and upward on the posterior aspect of the left ventricle, and gradually faded into the muscle wall. The second branch was quite

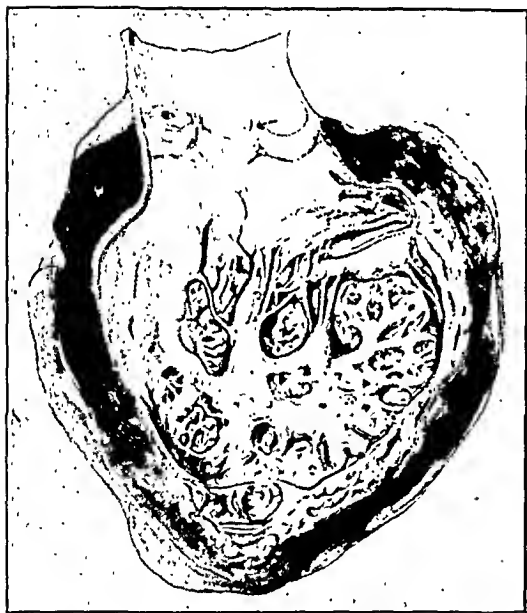


Fig. 3.

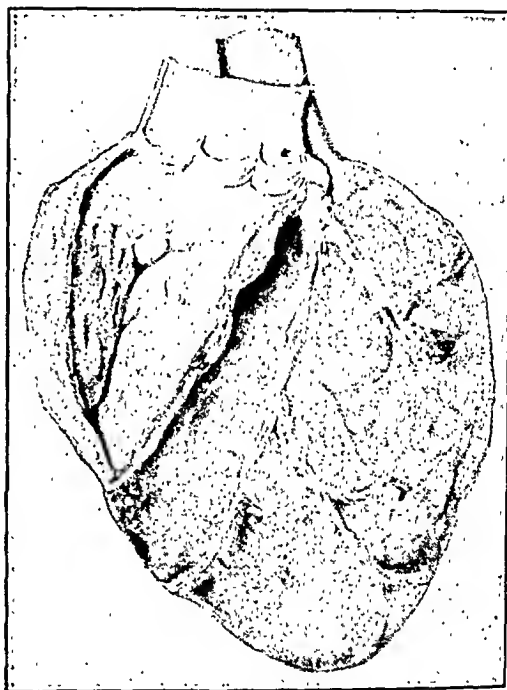


Fig. 4.

Fig. 3.—A drawing showing the well marked hypertrophy and dilatation of the left ventricle. The right coronary orifice is seen above the right aortic valve. (For this and subsequent drawings we are indebted to Miss Dorothy Norton.)

Fig. 4.—Showing the relatively small size of the opened right ventricle. The orifice of the left coronary artery is seen above the left pulmonary cusp.

small and supplied the upper part of the left ventricle. The inferior vena cava at its point of entry into the right auricle also communicated with the left auricle by a narrow slitlike opening 3 mm. in length. The ductus arteriosus was slightly patent at the aortic end, but was completely occluded as it approached the pulmonary artery.

The microscopic examination of the tissues was made by Dr. Tracy B. Mallory.

The greatly increased thickness of the heart wall was due in part to an increase in the number of muscle fibers, and in part to the separation of the muscle bundles by unusually large spaces, the result of vascular dilatation together with a small amount of fibrosis between the bundles. The average width of the muscle fibers was no greater than that of a control section from an infant nine weeks of age. Sections taken from the wall of the right and of the left ventricle showed

no appreciable differences in the size of the muscle fibers. However, on the endocardial surface of the left ventricular wall there was marked fibrous thickening with occasional patches of fibrosis at deeper levels. A considerable proportion of the muscle cells showed two and three nuclei in close proximity or even in contiguous chain formation, strongly suggestive of the chains of nuclei seen in degenerating skeletal muscle attributed to amitotic nuclear division. Careful search failed to reveal mitotic figures. In a few areas groups of vacuolated muscle cells with large pale nuclei were seen, presumably "hydropic" degeneration since fat stains were negative.

The greater part of the lung sections showed markedly thickened alveolar walls. In some areas the lung tissue was not recognizable, the appearance being that of a mass of small darkly stained nuclei surrounded by thick fibrils and infiltrated with monocytes. In the center of one of the masses a small bronchiole could be seen. The arterioles were very thick and their lumina were almost obliterated.

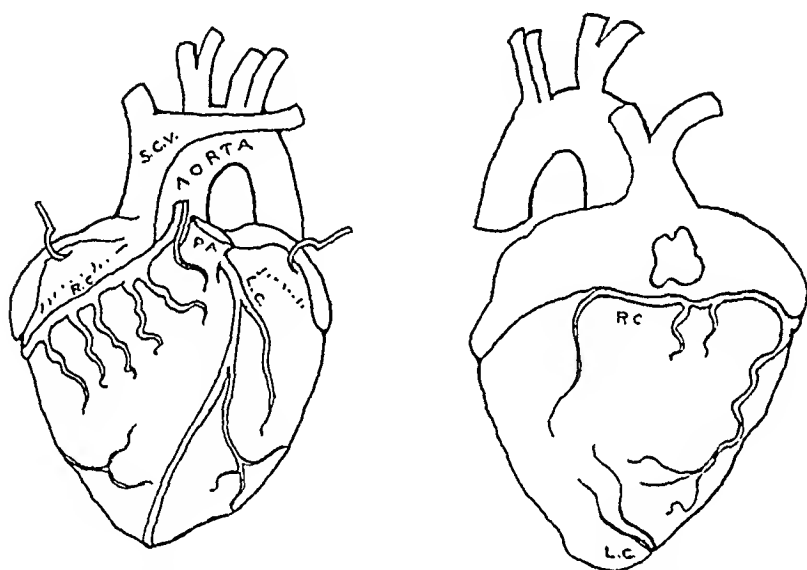


Fig. 5.—Drawings showing the origin and distribution of the right and left coronary arteries, the latter arising from the pulmonary artery.

The kidney sections were normal. The liver showed marked vacuolization and a moderate destruction of cells.

The anatomical diagnosis was congenital cardiac hypertrophy, congenital anomalies of the coronary arteries and the inferior vena cava, and fibrosis of the endocardium of the left ventricle.

DEVELOPMENTAL ANOMALIES OF THE CORONARY ARTERIES

Although little is known concerning the development of the coronary vessels in the human embryo, presumably it is similar to that which takes place in other mammals. According to Martin³¹ the first anlage of the future coronary artery in rabbits is a club-shaped bud which makes its appearance from the endothelial surface of the bulbous arteriosus about the twelfth day of embryonic life and before this common trunk has been divided by the so-called spiral septum into the aorta and pulmonary artery. Lewis³² states that the coronary bud appears nearer the fourteenth day. The anlage for the

left coronary artery is first formed, and somewhat later that for the right makes its appearance. Grant¹⁴ has more recently reviewed the entire subject and states that "indications of the coronary arteries appear as thickenings of the aortic endothelium in embryos (rabbits) of 10-11 mm. greatest length. Here again, there is some variation. In this series an endothelial bud corresponding to the left artery is seen in specimens of 10, 11, 11.5 mm. in length; in another specimen of 11 mm. no arterial bud is to be found, but both right and left buds are present in a second 11.5 mm. embryo. Figure 7 shows the commencement of the right coronary in a 11.5 mm. embryo—the stage

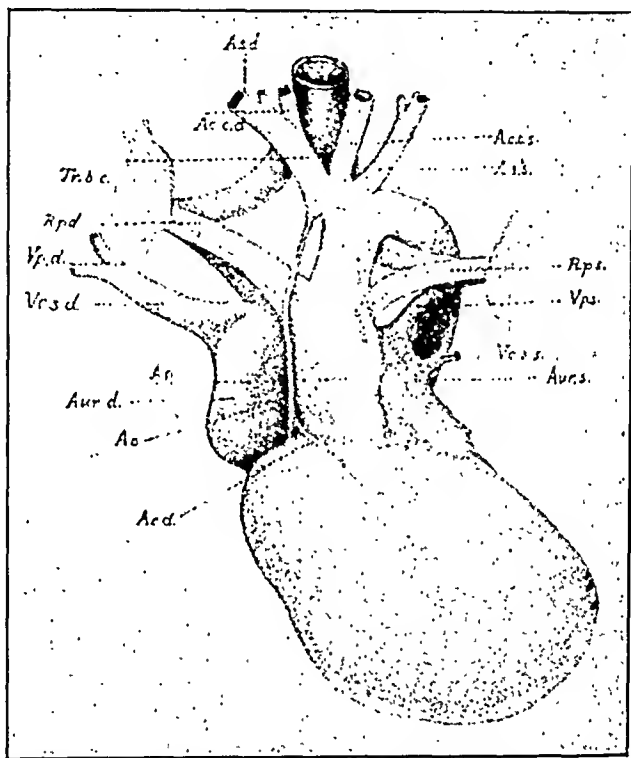


Fig. 6.—After Konstantinowitsch, showing the origin of the right coronary artery from a rudimentary aorta (Ao). The origin of the left coronary from the pulmonary artery is not shown in the diagram. (Prag. med. Wehnschr. 1906.)

at which the truncus communis is being separated into aorta and pulmonary artery by the growth of the endothelial cushions. The arterial rudiments are first solid columns of cells which later acquire a lumen and grow outward into the superficial portion of the myocardium."

Congenital abnormalities of the coronary vessels may exist as isolated pathological curiosities of no clinical significance; as such they usually remain entirely unsuspected until discovered in the course of a post-mortem examination. True anomalies of the coronaries are not commonly associated with extensive developmental defects in the heart or great vessels other than transposition of the great trunks or

situs inversus of the heart. Occasionally the coronary anomaly itself may be of considerable importance and its relationship to certain cases of congenital hypertrophy of the heart is of interest. The observed cases of variation in the coronary vessels are sufficiently infrequent and yet important enough to warrant a brief review of the subject. They may be grouped under two main headings: (a) Abnormalities of origin; (b) Variations in number, size, and distribution.

Abnormalities of Origin.—The origin of one of the major coronary stems from the pulmonary artery unassociated with other significant developmental defects is rare. We have encountered reports of only 8 cases in addition to the one we are recording of this unusual arrangement. It is obvious that because of the extensive co-existent vascular defects the cases recorded by Konstantinowitsch and Dreyfuss which are to be commented upon later do not properly belong in this small group. In 1911 Abrikosoff² reported the first case in a five-and-one-half-months-old infant who died of pneumonia. Autopsy revealed well marked cardiac enlargement due in part to an aneurysmal dilatation of the left ventricle. The right coronary arose in the usual place, but the left took origin from behind the left leaflet of the pulmonary artery from an ostium that was slightly wider than normal. The vessel divided and had the usual distribution of an otherwise normal left coronary artery. The anterior wall of the left ventricle near the apex was completely replaced by a transparent fibrous tissue membrane of only 0.5 mm. thickness in its central portion and which extended over an area about 2 cm. in diameter. Small areas of calcification were present and the vessels to this part showed a definite endarteritis, but without obliteration of the lumen, which was interpreted as being a process coincident with, rather than a possible cause of the myocardial degeneration. It was further noteworthy that the fibrous tissue replacement of the wall was maximal in the region supplied by the descending ramus where anastomotic connections with the right coronary artery are minimal. There were no other congenital defects present. The case of Heitzmann¹⁹ (1916) was identical and occurred in a three-and-one-half-months-old female infant who died with cyanosis and syncope. Here, again, the right coronary was normal, but the left arose in the left sinus of Valsalva of the pulmonary artery. There were marked fibrosis and thinning of the wall of the left ventricle as well as of the anterior papillary muscles; the latter contained areas of calcification. A diffuse endocardial thickening of the septum and marked aneurysmal dilatation of the left ventricle were present as well as enlargement of the heart as a whole. The author was impressed by the striking similarity of this picture to that observed in older people with myocardial infarction and fibrous tissue replacement resulting in aneurysmal dilatation of

the wall, and dependent upon preceding coronary sclerosis and occlusion. Kiyokawa's patient²⁴ lived four months. The clinical course was identical with ours in that for the first few weeks the child was entirely normal. Death occurred after several weeks during which frequent attacks of dyspnea, cyanosis, and convulsions occurred. The heart was greatly enlarged, and the wall of the left ventricle supplied by the anomalous left coronary was reduced to a thickness of 1 mm. The endocardium of the left ventricle showed the usual marked hyperplasia.

The remaining cases have not shown such marked degrees of myocardial fibrosis, but here again the degenerative changes have been of a similar nature. The case recorded by Scholte⁴¹ of a two-and-one-half-months-old female who died of bronchopneumonia showed post mortem well marked cardiac enlargement. The right coronary artery arose at its normal site, but the left sprang from the left sinus of the pulmonary artery. There was marked fibrosis of the myocardium of the left ventricular wall, together with fatty degeneration of the muscle fibers, areas of necrosis and calcification, and a diffuse thickening of the endocardium of the left ventricle. It is of interest that the most extensive changes here occurred nearer the endothelial than the pericardial surface of the ventricular wall, a situation analogous in some respects to that observed after coronary occlusion where the area of infarction is usually of greatest extent near the endothelial surface and dependent, no doubt, upon the relatively scant vascular supply and anastomotic connections of this portion of the wall. The patient of Carrington and Krumbhaar⁶ lived twelve months. The heart showed well marked hypertrophy and no gross difference in the appearance of the two ventricles. The left coronary arose from the pulmonary artery just above the posterior cusp and nourished much less than half of the heart, a fact which perhaps accounted for the relative longevity of the case. In sections from the area supplied by the misplaced vessel there was a distinct increase of interstitial fibrous tissue, rather diffuse and here again more marked near the endocardial section of the wall. The parenchymatous degeneration (loss of striae and vacuolization) was also most marked in the areas supplied by the anomalous artery, the walls and lumen of which were normal. In discussing the etiology of the congenital hypertrophy in this case the authors felt that the rôle of the abnormal coronary and the myocardial fibrosis, though thought by them unimportant, must be considered as possible etiological factors. Stevenson's instance (cited by Abbott)⁴⁵ is similar and occurred in a three-months-old infant; the excessive hypertrophy and dilatation of the left chambers were extensive enough to produce atelectasis of the lung, hoarseness, and difficulty in passing a feeding tube.

In exceptional instances patients have attained adult age in spite of this apparently serious variation in the coronary vessels, and in striking contrast to the cases noted above is the picture presented by Abbott's remarkable patient,¹ a woman aged sixty-four years who died accidentally. Gross hypertrophy and extensive fibrosis of the myocardium were present. The right coronary arose in the usual place by a much dilated orifice and expanded directly into a huge thick-walled loop the size of a crab apple which projected 2.5 cm. above the subepicardial fat. Descending branches as well as the main trunk of the vessel were wide thick-walled tortuous channels. No coronary arose from the usual site of the left, but instead a large patulous opening lay in the floor of the dilated posterior sinus of Valsalva of the pulmonary artery and from this opening sprang a large thin-walled trunk of venous character which divided 1 cm. beyond into two large branches which followed in general the course of the branches of a normal left coronary. The descending branch expanded into a large triangular shaped sinus 2 cm. in diameter at its widest portion. In the floor of this sinus were several thick-walled septa behind which large vessels opened into it from the myocardium, strongly suggesting that the course of the blood was toward the pulmonary artery, a view also shared by Brooks⁵ who had previously encountered two cases in which an accessory coronary vessel arose from the pulmonary artery and meeting the branches from the two aortic coronaries produced a remarkable anastomosis of a circoid character. A case mentioned by Krause²⁶ is in some respects analogous; and more recently Feriz¹⁰ has recorded similar instances. In this particular accessory coronary group the extra vessel is relatively small and probably of no importance in the nourishment of the heart, since it seems likely that the direction of the blood flow in the anomalous vessel is toward the pulmonary artery. Finally, the eighth case, that mentioned by Sehley,⁴⁰ is unique in that it is the only instance where the malposed vessel originating from the pulmonary artery was the right coronary; furthermore, there was no evidence of a reversal of flow and aneurysm formation or of myocardial fibrosis. The patient was a sixty-one-year-old laborer who died with auricular fibrillation and congestive failure. At autopsy there was evidence of cardiovascular lues; insufficiency of the aortic leaflets, aortitis, and aneurysmal dilatation of the ascending aorta. The right coronary arose above the right valve of the pulmonary artery. The left coronary artery arose at its normal site but supplied a larger portion of the heart than is usual. There were no gross anastomoses between the two vessels. A careful histological examination of the wall of the two ventricles showed no alterations such as have been noted in the other seven recorded cases, and there was no evidence that the abnor-

mal coronary had either handicapped or shortened this man's life even though portions of the myocardium must have been nourished in part by insufficiently aerated blood.

There appear to be two possible explanations to account for this interesting variation in the origin of one or other of the coronary arteries. The most likely background for this anomaly, as has been pointed out by others, would seem to be a faulty arrangement of the primitive endothelial buds before the division of the truncus arteriosus has occurred, so that one or the other is misplaced to the portion of the common trunk destined to become the pulmonary artery. On the other hand, although the *anlagen* of the coronary vessels may be in their proper place, the position taken by the spiral septum may be at fault, the division taking place too far to the right, thereby including one of the coronary buds in the pulmonary portion of the dividing trunk. Support is lent to this last hypothesis by the case of Konstantinowitsch where the division of the truncus arteriosus was obviously abnormal.

Minor variations in origin of the coronary arteries, usually from a higher level in the aorta, are not infrequently encountered and when unassociated with other defects are unimportant. Giepel¹³ records a case in which the right coronary artery arose from the ascending aorta 7 mm. above the cusp margins. Hyrtl²¹ mentions an instance where the right artery arose near the origin of an abnormal artery thymica 16 mm. above the right aortic sinus, and in Schrader's case¹² the right coronary arose 18 mm. above the cusp margins of an otherwise normal heart. More extensive so-called misplacements have been noted where one or other coronary artery arises from the arch of the aorta, the innominate, or even from a carotid artery. Farre⁹ in 1814 described a *cor biloculare* in a male infant of seventy-nine hours from whose ventricle arose a single arterial trunk which first gave off two large pulmonary branches and continued on to give origin to the innominate, the left carotid and the left subclavian arteries. It also sent downward a single artery to the heart wall which appeared to be its only coronary supply. The continuation of the main arterial trunk had the usual appearance of the descending aorta. Forster's case¹¹ is identical, and here again the abnormal vessel appeared to furnish the sole blood supply to the heart. In Jürgen's specimen,²² the description of which is brief and inadequate, a right coronary artery is said to have arisen from the arch of the aorta. Somewhat analogous is the patient of Owen-Clark,³⁴ the case of the *cor triloculare biatriatum* of a two-and-one-half-day-old female infant, in which a single arterial trunk arising from the ventricle was entirely void of coronary connections at the normal sites, but gave off two pulmonary branches, a short innominate trunk from which the carotids and the

right subelavian took origin, as well as a small artery which descended to the interspace between the large arterial trunk and the right auricle having the appearance of a rudiment of the ascending aorta and furnishing the coronary arteries. The case of Vernon⁴⁸ is similar in that the point of origin was from the innominate. In the instance mentioned by Power-Heath (cited by Peacock³⁸) the coronary artery was cut across but apparently arose from the aorta or one of its branches; whereas Pitschel³⁶ and Mayer³² found the origin of a right coronary artery from the carotid artery, and in Tow's case⁴⁷ a single vessel from a pulmonary branch of the common arterial trunk was distributed to the heart and appeared to be its only source of blood supply.

Konstantinowitsch³⁵ appears to have been the first to suspect the true nature of the majority, and perhaps all, of the above cited cases, from Farre through Tow, of so-called high origin of a coronary artery; and furthermore, because of the important evidence furnished by his remarkable case as related to a possible explanation cited above of the abnormal origin of coronary vessels from the pulmonary artery, the description and diagram of his specimen is given. A two-day-old female infant dying with the signs of cyanosis and collapse showed at autopsy a cor biloculare with a rudimentary aorta, completely stenosed at its origin at the base of the ventricle, but giving rise to the right coronary artery, the blood to which passed down the patent stem of the rudimentary aorta from its connection with the innominate (Fig. 6). The left coronary artery arose from the large trunk designated the pulmonary artery. The author believed that here the misplaced origin of the left coronary was dependent upon the obviously abnormal division of the truncus arteriosus. Furthermore, attention was called to the fact that in the so-called "high origin" of the coronary artery of those cases where the aorta appears as a rudimentary vessel a similar interpretation may apply, so that instead of a true high origin the coronary actually arises at an approximately normal level from a rudimentary ascending aorta. This conception, shared by Rauchfuss³⁹ and also by Abbott¹ who has recorded a case of atresia of the ascending aorta with coronaries from the blind lower end, would indicate a single direction in these cases otherwise difficult to explain on a reasonable embryological basis; and would include further the cases recorded by Kussmaul,²⁸ Taruffi⁴⁶ and Schrader⁴² (an additional case, not the one already referred to). In the last mentioned case both coronaries were given off from the rudimentary aorta as separate vessels. Recently Dreyfuss⁷ has described a case similar in many respects to that of Konstantinowitsch of a cor biventriculare triloculare in which there was stenosis of the rudimentary aorta. Here, also, the left coronary artery arose from the large pulmonary trunk.

Variation in Number, Size, or Distribution.—Less important anomalies in the arrangement of the coronary vessels are chiefly those involving a variation in number or distribution. Normally the coronaries arise from the right and left sinuses of Valsalva above the corresponding semilunar valves of the aorta. Rarely both arteries may arise from a single stem or from adjacent openings in the same sinus.^{4, 8, 20, 35, 37, 43} Usually the primary branches from the single stem follow the customary course of the right and left arteries respectively, but in Plaut's case³⁷ as well as in that of Petré,³⁵ there was no vessel found which from its position or direction could be considered a counterpart of the absent right coronary artery, and in the instance mentioned by Engelmann⁸ only a small rudimentary vessel arising from the single large left coronary had any resemblance to the right vessel, but a large and entirely abnormal branch of the descending ramus coursed downward over the right ventricle nearer the apex than the auricle and appeared to be the chief supply to the right side of the heart. An interesting complication has been recorded by Smith and Graber⁴³ of a typical coronary thrombosis in a forty-six-year-old man who died of subsequent congestive failure. The blood supply to the entire heart was furnished by a single large artery which during its early course corresponded in location with that of the right coronary artery. Later branches were given off which resembled in a diminutive manner the descending and circumflex branches of the left coronary artery. The difference between the size of these vessels and that of the usual two main branches of the left coronary artery was striking. The blood supply to the left ventricle was thus apparently much less than in the normal subject, and it was difficult to understand how the blood supply in this instance permitted the individual to perform the heavy physical work to which he was accustomed.

More frequently the number of coronaries is increased to three and very rarely to four.^{3, 5, 10, 12, 16, 17, 23, 26, 30, 33, 50} The accessory arteries are small and as a rule arise a short distance from the origin of one of the main coronary stems and in general are distributed along a course analogous to that of a branch of the main vessel, so that occasionally the circumflex branch of the left coronary arises as a separate vessel from the left sinus. In several cases already noted^{5, 10, 26} the accessory vessel arose from the pulmonary artery. Krause in Henle's *Handbook of Anatomy*²⁰ mentions a compensatory widening of the distribution of one vessel associated with an unusual decrease in the size of the other. In the presence of complete atresia of the pulmonary orifice the coronaries may dilate and send anastomotic branches contributing to the collateral circulation through the lungs. In the interesting case cited by Voss⁴⁹ the patient reached the age of thirty-seven years in spite of a

completely closed pulmonary artery. An adequate collateral circulation to the lung was maintained chiefly by four bronchial arteries arising from the descending aorta and anastomosing with branches from both coronary arteries which pursued a tortuous course to be distributed to the circulation through the lungs. A curious variation of the coronary circulation occurred in Grant's case,¹⁵ in which blood filled spaces in the right ventricular muscle formed a nodule 6 mm. in diameter and communicated freely with the cavity of the ventricle and with the coronary arteries and veins. The malformation was interpreted by the author as representing a persistence and growth of the intertrabecular spaces of the compact myocardium which are normally reduced to capillaries. Ingleby's case mentioned by Abbott¹ is analogous. A unique case was encountered by Halpert¹⁶ as an incidental necropsy finding in a male adult and consisted of an arteriovenous communication between the right coronary artery and the coronary sinus with aneurysmal dilatation of the parts involved.

COMMENT

The structural alterations occurring in the heart wall of the small series of reported cases where one of the coronary arteries arises from the pulmonary artery are important and give rise, with the one exception noted,⁴⁰ to a characteristic pathological picture of well marked myocardial degeneration, in some cases even to the extent of complete fibrous tissue replacement in the region supplied by the anomalous artery, with resulting aneurysmal dilatation of the ventricular wall. In addition to the greater or lesser local changes, there is well marked hypertrophy of the heart as a whole which probably represents a compensatory mechanism. Death within the first year of life is the rule. One must assume, we believe, that these parenchymal changes are dependent in large part upon two factors: (1) the inadequate nourishment of the ventricular wall by *venous blood* and (2) the relatively low pressure in the coronary artery arising from the pulmonary artery. It is of interest further to note the striking similarity of the varying degrees of degenerative changes encountered in this series of cases to those arising as a result of an inadequate blood supply secondary to coronary sclerosis and narrowing in adults where one finds in the more advanced cases complete occlusion, myocardial infarction, and eventual fibrous tissue replacement of the wall. It is evidently of some clinical importance that in our case, which appears to have been the only one in which an electrocardiographic study was made, the tracing showed the unmistakable sign which we have come to associate with important coronary disease in adults; namely, a deep and late inversion of the T-wave in all three leads, together with the supportive evidence of low voltage of the QRS complexes. It is of interest that such was not the case in a recently reported instance of uncomplicated and idio-

pathic congenital hypertrophy in an infant seven months old whose electrocardiogram was normal in all respects.⁴⁴

In retrospect when we consider the grossly abnormal and qualitatively inadequate blood supply of the left ventricular wall resulting in myocardial ischemia with subsequent degenerative changes, together with the electrocardiographic finding of a "coronary" type of T-wave, it seems probable that in this infant the curious attacks of paroxysmal discomfort, precipitated by exertion and accompanied by a profound reflex vasomotor disturbance, were those of angina pectoris. If this be true, it represents the earliest age at which this condition has been recorded. An explanation for the freedom from symptoms during the early weeks of life remains obscure. The necropsy finding of slight patency of the aortic end of the ductus botalli suggests the possibility that it may not have become occluded until several weeks after birth, thereby permitting the admixture of arterial with venous blood in the pulmonary artery, but of this we have no proof.

It is suggested that in future cases of uncomplicated and unexplained cardiac enlargement in infancy the finding of a similar electrocardiographic picture in the absence of abnormal axis deviation or toxemia may indicate an inadequate and anomalous coronary supply to the heart.

SUMMARY

An instance is recorded, in a male infant dying at the age of three months, of an abnormal origin of the left coronary artery from the pulmonary artery, associated with marked enlargement of the heart (due to hypertrophy and dilatation of the left ventricle), together with extensive degenerative changes in the ventricular wall supplied by the malposed vessel. In view of these findings, it is probable that the paroxysmal attacks of acute discomfort precipitated by exertion and associated with profound vasomotor collapse occurring in this infant were those of angina pectoris. The electrocardiographic picture in our case was similar to that seen in adults with important coronary disease. In the few recorded cases (8 in number in addition to our own) of this rare anomaly a characteristic pathological picture has resulted. Death within the first year has been the rule. Two of the cases have been exceptional.

A review of congenital variations in the coronary vessels and a discussion of their embryological background are included. A bibliography is appended.

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ANOMALOUS ORIGIN OF THE LEFT CIRCUMFLEX CORONARY ARTERY*†‡

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WITH increasing interest in and knowledge of the clinical and pathological picture of coronary artery disease, anatomical studies of the normal distribution and variations of the blood vessels of the heart are assuming greater significance than heretofore.

Variations in the coronary arteries may be considerable in reference to their origin, course, distribution and anastomoses. Anomalies of the coronary arteries may at times have clinical importance, as illustrated in the cases described by Abrikossoff,¹ Carrington and Krumbhaar² and Scholte³ in which one of the two coronary arteries arose from the pulmonary artery. Death occurred in the early months of life due to myocardial failure associated with myocardial degeneration of that portion of the heart (left ventricle) supplied by the anomalous vessel.

NORMAL DISTRIBUTION OF THE MAIN CORONARY ARTERIES

A short résumé of the usual origin and distribution of the main coronary vessels will aid in the understanding of the anomaly to be described. The average normal human heart is supplied by two coronary arteries. The left coronary artery arises from the left sinus pocket of the aorta and divides about a half centimeter from its origin into two branches, an anterior descending and a circumflex branch. The right coronary artery arises from the right sinus pocket of the aorta and emerges between the roots of the pulmonary artery and aorta, pursuing its course to the right along the auriculoventricular sulcus up to and usually beyond the crux§ of the heart posteriorly. The terminal branches of the right coronary artery supply the posterior part of the right ventricle and part of the posterior portion of the left ventricle. (Fig. 1.)

ANOMALOUS CORONARY ARTERY

In the cases presented in this report, the right coronary artery and the left anterior descending branch of the left coronary artery of the

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§Crux: That situation of the heart posteriorly where the auricles and ventricles meet. (Gross.⁴)

heart have their normal origin, course and distribution. The left coronary artery, however, does not give rise to the circumflex branch.

In three of the four cases studied, the left circumflex coronary artery takes its origin directly from the aorta in the right sinus pocket, just posterior to the mouth of the right coronary artery, and in one case from the main right coronary artery. The vessel equals in caliber that of the main coronary arteries. It proceeds backward and to the left for a short distance, between the root of the aorta and the right auricular

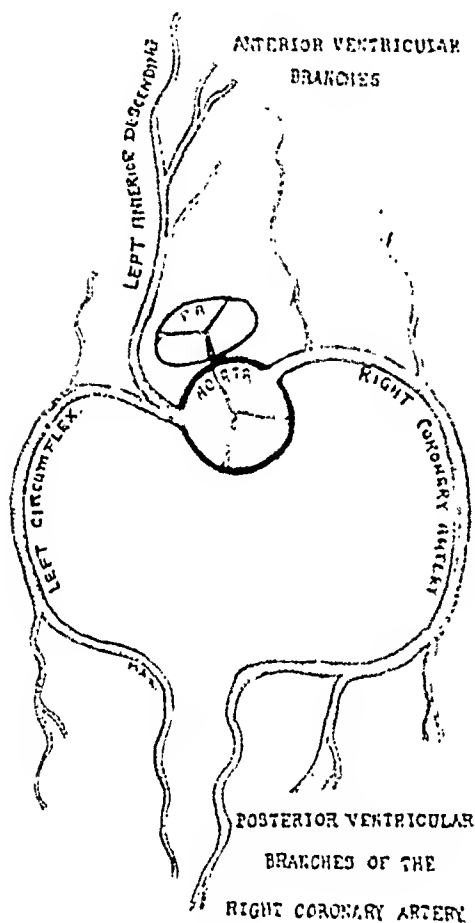


FIG. 1.

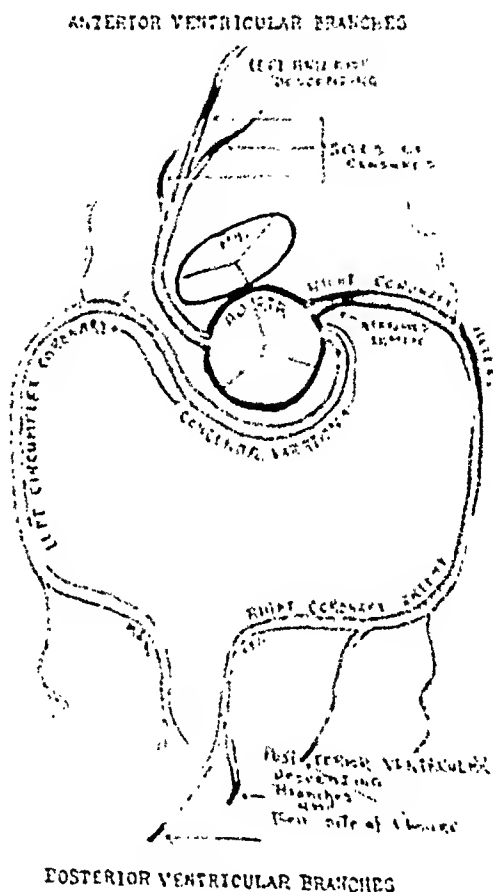


FIG. 2.

Fig. 1.—Diagram of normal origin and distribution of the main coronary arteries. The vessels are spread out on a flat plane.

Fig. 2.—Diagram showing origin and distribution of the left circumflex coronary artery in the case which presented multiple occlusions in the ramifications of the left anterior descending branch and in the posterior ventricular branches of the right coronary artery.

appendage, just above the interventricular septum, hugging closely the posterior portion of the aorta at its root. It then circles anteriorly to emerge between the root of the aorta and the left auricular appendage in the auriculoventricular sulcus of the left side, and for the rest of its course occupies the bed normally held by the left circumflex coronary artery. (Figs. 2, 3 and 4.)

ANASTOMOSES BETWEEN THE ANOMALOUS VESSEL AND THE OTHER CORONARY ARTERIES

The anomalous vessel anastomoses with the other coronary arteries in four different areas. (Fig. 3.)

A. The artery gives rise to descending branches supplying the anterior and lateral third of the left ventricle. Some of these branches anastomose with the branches of the left anterior descending coronary artery. (Area I, Fig. 3.)

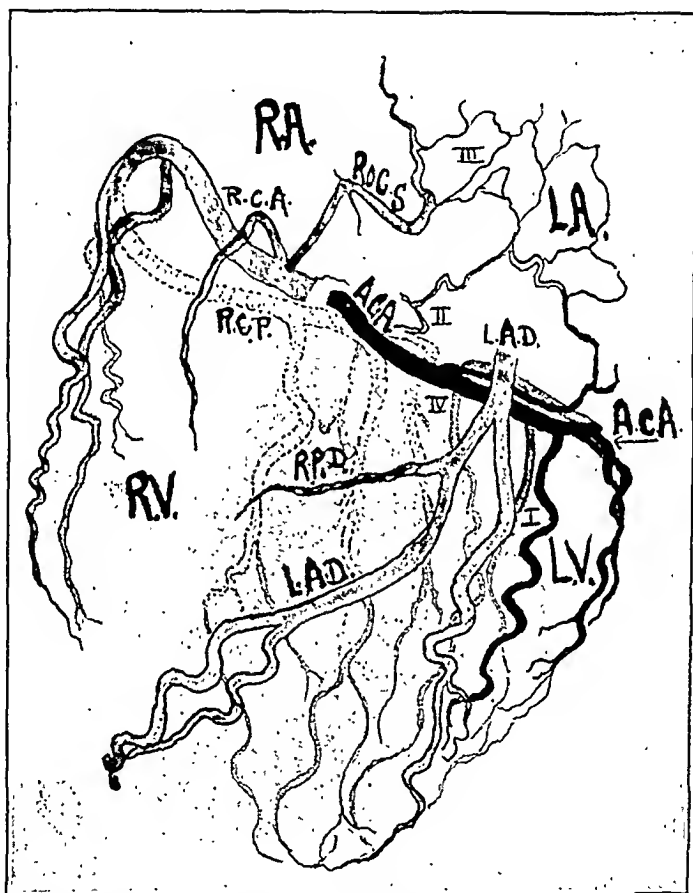


Fig. 3.—Semidiagrammatic sketch of retouched roentgenogram of injected heart (anterior view) showing the origin, course, distribution and areas of anastomoses of the anomalous left circumflex coronary artery. (Shaded black) A.C.A., anomalous left circumflex coronary artery; L.A., left auricle; L.A.D., left anterior descending branch; L.V., left ventricle; R.A., right auricle; R.C.A., right coronary artery; R.C.P. and R.P.D., posterior ventricular branches of the right coronary artery; R.V., right ventricle. Numerals I, II, III, and IV indicate areas of anastomoses.

B. In its course along the auriculoventricular sulcus posteriorly, it also gives off branches which anastomose with the posterior descending branches of the right coronary artery. (Area IV, Fig. 3.)

C. It gives off a branch near its origin which circles to the left and upward in the substance of the left auricle passing over its dome to reach its posterior wall where near the crux of the heart it anastomoses by its smaller branches with the branches of the posterior portion of the right coronary artery. (Area II, Fig. 3.)

D. On its way up the anterior wall of the left auricle the above mentioned branch sends many twigs upward and to the right toward the mouth of the superior vena cava where its ramifications anastomose profusely with the smaller branches of the artery to the sino-auricular node. (Area III, Fig. 3.)

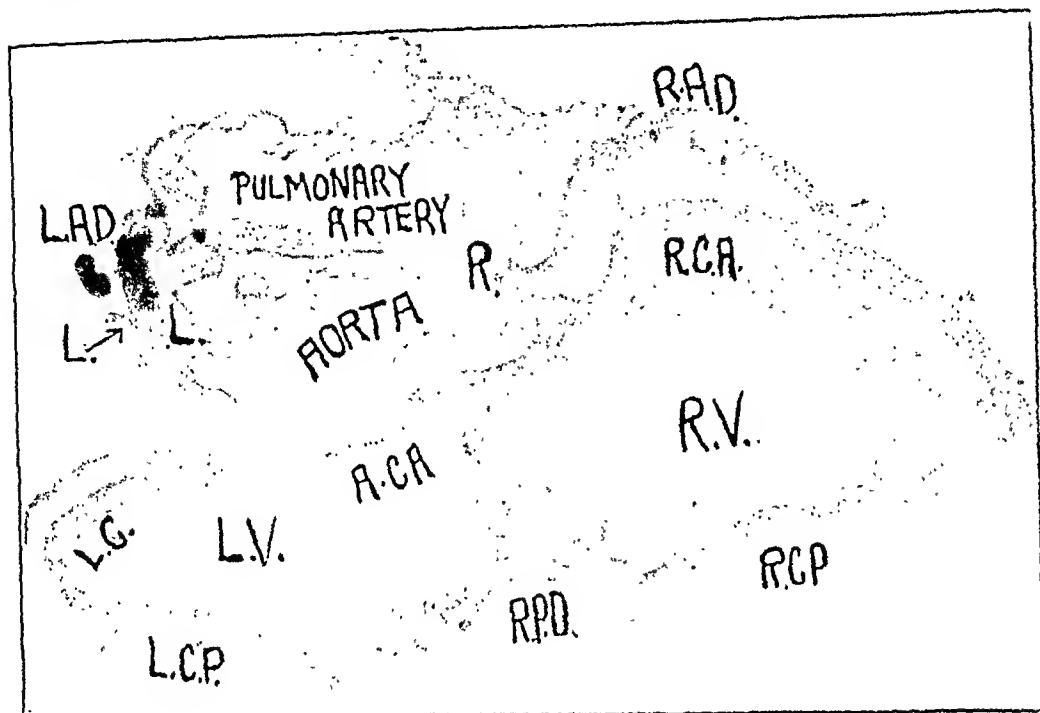


Fig. 4.—Roentgenogram of cross-section of injected heart near the base, showing the origin of the anomalous left circumflex coronary artery (A.C.A.), from the right coronary artery (R.C.A.). L.A.D., left anterior descending branch; L.C.P., posterior ventricular branches of the left circumflex coronary artery; R.C.P. and R.P.D., posterior ventricular branches of the right coronary artery; R.A.D., anterior descending branch of the right coronary artery.

DISCUSSION AND SUMMARY

Four hearts have been studied in which there was an anomalous origin and course of the left circumflex coronary artery. In each heart the left anterior descending branch and the right coronary arteries had their normal origin and distribution. In three hearts the left circumflex coronary artery arose directly from the right sinus of Valsalva, immediately posterior to the origin of the right coronary artery. It then pursued its course posteriorly to the root of the aorta and finally emerged anteriorly between the root of the aorta and the left auricular appendage around the margo obtusus in the auriculoventricular sulcus.

In the fourth case the left circumflex coronary artery arose as a branch of the right coronary artery one centimeter from its ostium. It then maintained a course similar to that described for the left circumflex coronary artery in the other three cases. A point of clinical interest in one of these cases is the fact that the left circumflex coronary artery was normal and patent throughout, whereas the right coronary

artery and the left anterior descending branch presented numerous occlusions (Fig. 2). The clinical history of this fifty-one-year-old man showed ample evidence of repeated attacks of coronary occlusion in the last three years of his life. It seems possible that the independent origin and distribution of the left circumflex coronary artery in this case may have served for a time as a compensating source of nutrition to the myocardium through its anastomoses.

We are indebted to Dr. Louis Gross for the aid he has given in these studies.

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PREMATURE BEATS PRODUCED BY THE MECHANICAL STIMULATION OF THE EXPOSED HUMAN HEART*

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THE observations of Barker, Macleod and Alexander¹ on the exposed human heart, with the analysis of the obtained data, have opened a wide field of controversy relative to the correct terminology to be used in describing premature beats and bundle-branch block. By electrical stimulation of various points on the ventricular musculature they produced premature beats which were recorded simultaneously on the three usual leads. They found in general, that stimulation of the right ventricle produced premature beats with a major deflection of the QRS complex upward in Lead I and downward in Lead III, while stimulation of the left ventricle yielded complexes with a major deflection downward in Lead I and upward in Lead III. These observations were not in accord with the current beliefs which had been largely based on animal experimentation. They suggested that the terminology of premature beats be revised (reversed) to conform to the new findings. They also concluded that electrocardiograms which had been previously thought to represent a block of the left bundle branch, were in reality records of right bundle-branch block and vice versa. Since their original observations, very little evidence has been added to prove or disprove their findings and theories.

Marvin and Oughterson² have recorded premature beats produced by electrical stimulation of the heart through a wound made for draining a pyopericardium. The points of stimulation on the right and left ventricles were later checked by post-mortem examination. Their findings confirmed those of the Ann Arbor investigators.

In a pericardiectomy³ mechanical stimulation of the right ventricle produced premature beats with a major deflection upward in Lead I and downward in Lead III.

In a recent article⁴ a case was presented in which an aneurysm of the sinus of Valsalva had nearly completely severed the left main branch of the bundle of His. There was also microscopic evidence of severe disease of the bundle above its bifurcation. The electrocardiogram showed an A-V heart-block and a right bundle-branch block (new terminology). The case was presented as supportive evidence for the original terminology of bundle-branch block. A critical analysis of the record presented, however, seems to show the tracing as that of a complete A-V heart-block with a coincident auricular rate nearly ex-

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actly twice that of the ventricles, rather than a two-to-one A-V heart-block as was the interpretation given.* If this be correct, the case has no bearing on the bundle-branch-block problem, and the conclusions of the author are not justified.

The wide exposure necessary for the removal of an adherent pericardium in a case of Pick's syndrome afforded an excellent opportunity for recording premature beats from known areas of the human heart.

CASE AND METHOD

An American boy, J. W., eleven years of age, was admitted to the Medical Service of Dr. Thomas McCrae for the fourth time in two years, on Nov. 2, 1932. He had been troubled with recurring ascites for nearly four years, which had become so severe in the past few months as to necessitate removal by paracentesis every two or three weeks. There was no past history or family history of rheu-

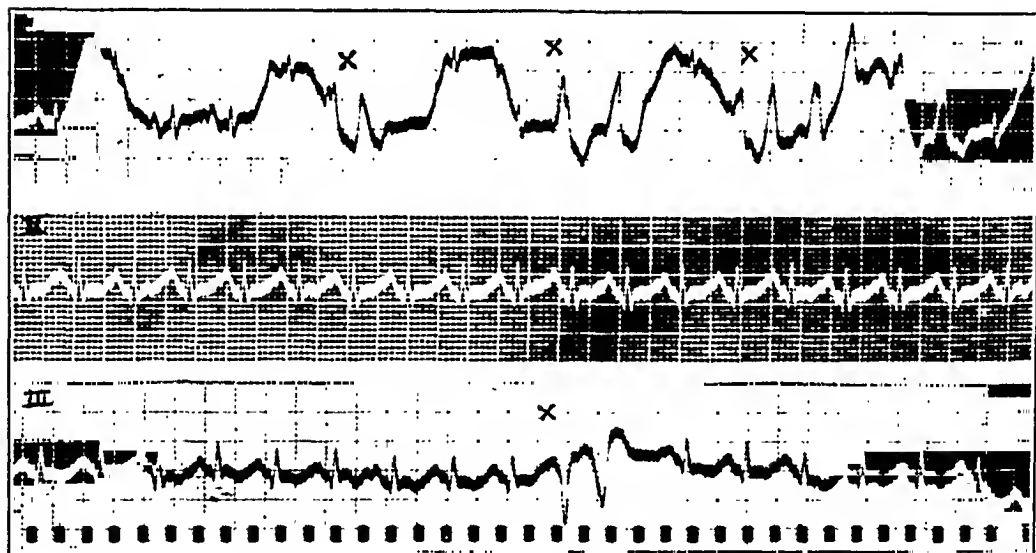


Fig. 1.—Electrocardiogram taken at operation. Leads I and III were taken in succession. Lead II was taken a few minutes later but is added to complete the record. The premature beats shown in Leads I and III were produced by direct mechanical stimulation of the anterior surface of the right ventricle. Time of stimulation marked "X". The main deflection of the QRS complexes of the premature beats is upward in Lead I and downward in Lead III, conforming to the new terminology.

matic fever or tuberculosis. Examination at this time showed an underdeveloped, poorly nourished boy. The venous distention of the neck and arms was striking. The heart was questionably enlarged to physical examination and showed no murmurs. The blood pressure was systolic 90 mm. and diastolic 72 mm. There was no pulmonary congestion or pleural fluid. There was marked ascites with an umbilical and right scrotal hernia. The liver edge was felt 5 cm. below the right costal margin in the midclavicular line and was rounded, smooth and not tender. The spleen was not palpable. Slight pitting edema of the feet and legs was present on admission. The venous pressure was 23 cm. of water (direct and indirect methods), measured at the antecubital fossa.

An x-ray study of the chest showed the heart shadow to be slightly enlarged to the right and left with stereoscopic and fluoroscopic findings suggesting an adherent pericardium.

*This opinion is held by several in addition to the author.

The electrocardiogram on Nov. 3, 1932, showed a normal sinus rhythm with no axis deviation. The P-R interval was 0.18 seconds. The QRS complex showed slurring and very low voltage in all leads. T-waves were iso-electric in Lead I, flattened and diphasic in Lead II and inverted in Lead III.

A diagnosis of Pick's syndrome (concretio pericardii) was made, and as the clinical course was downhill, exploratory operation was advised. On Nov. 11, 1932, Dr. John B. Flick exposed the heart by removing the third, fourth, fifth, sixth and seventh left costal cartilages with a portion of the sternum. The heart was found to be approximately normal in size and its position in the chest was normal. There was an adherent pericardium present with several calcareous plaques, especially in the epicardium of the auricles. During the freeing and removal of the pericardium, it was noted the premature beats were easily elicited by manipulation or touching the heart with any instrument. Electrocardiograms were taken at intervals during the operation and showed premature beats from various foci. At the close a separate record was taken while stimulating a definite area of the heart musculature.

A portable electrocardiograph was used adjacent to the operating table and the time of stimulation noted verbally, the premature beats being observed by the surgeon and on the galvanometer string shadow. Leads I and III were taken in succession. Owing to the long duration of the operation and the condition of the patient, time permitted only the recording of premature beats from one area of the heart. The middle portion of the anterior surface of the right ventricle was chosen because of its accessibility and accuracy of localization. This corresponded to the area of points 6 and 7 in Barker, Macleod and Alexander's case. Several premature beats were recorded in Lead I by touching the heart with a forceps. The irritability of the muscle was such that they were easily produced, two or three premature beats in succession being recorded at times. Only one stimulation of the heart was done on Lead III, two successive premature beats being produced as is shown. The records of Leads I and III taken during the stimulation are presented. Lead II, taken a few minutes later, is included to make the electrocardiogram complete. The undulatory base line in Lead I was present only while the chest was open and is probably of respiratory origin.

CONCLUSIONS

The interpretation of the electrocardiogram published in a recent article is questioned as are the conclusions drawn from the case.⁴

A case is reported in which mechanical stimulation of the anterior surface of the right ventricle of the exposed human heart produced premature beats with a major deflection of the QRS complex upward in Lead I and downward in Lead III.

Further evidence is added in support of the correctness of the new terminology for premature beats and bundle-branch block, suggested by Barker, Macleod and Alexander.

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THE RELATIONSHIP OF ANGINA PECTORIS TO AORTIC VALVULAR DISEASE*

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ANGINA pectoris is not uncommonly associated with disease of the aortic valves. In the majority of such cases, the relationship is a causal one. The specific pathogenesis is usually an obstruction of the coronary ostia by lumatic or sclerotic stenosis or by endocarditic vegetations.

Certain cases, however, such as those described by White and Mudd,¹ may show no apparent obstruction of the coronary circulation. These have been explained as being due to the low diastolic pressure of aortic regurgitation, in the presence of which the coronary perfusion pressure is insufficient to maintain an adequate blood supply to the myocardium. Under the circumstances, the occurrence of angina would be favored and in certain instances might depend entirely upon this factor. Recent textbooks^{2, 3} have therefore included a low diastolic level among the causes of angina pectoris in cases of aortic insufficiency.

The experimental basis for this view is found principally in the work of investigators who believe that the coronary blood flow is determined largely by the aortic perfusion pressure. Smith, Miller and Graber⁴ state that coronary flow depends chiefly upon the height of the diastolic pressure. Anrep and his coworkers^{5, 6} found in the heart-lung preparation on dogs, that the mean arterial pressure was the most important value in the maintenance of an adequate coronary circulation. Both groups agree that the myocardial blood flow is significantly diminished by a lowering of the diastolic level as in aortic insufficiency.

Anrep, Davis and Volhard⁷ have further maintained that cardiac systole inhibits the coronary blood flow and that the principal flow through the myocardium occurs during diastolic relaxation. An actual backflow of blood during systolic contraction was demonstrated on the isolated perfused heart by Rössler and Paseual.⁸ It is therefore concluded that the arterial pressure during systole is not directly effective in the perfusion of the coronary vessels and that the myocardial circulation is diminished by factors such as an increase in pulse rate, which tend to shorten the duration of diastole. If these views be true, it is evident that the low diastolic pressure of aortic regurgitation must be

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an aggravating factor in the incidence of angina pectoris and may, per se, sometimes be sufficient cause for its occurrence.

Hochrein and Keller,⁹ however, have recently contested this view. Using more sensitive methods and working on intact dogs with normal respiration and with the coronary vessels unopened, they found that the coronary blood flow is maximal, not in diastole but in systole. In experimental aortic regurgitation, the height of the diastolic pressure was without influence upon the coronary circulation. Support for the validity of these conclusions is found in the work of Keller, Loeser and Rein¹⁰ who have shown that the blood flow through tetanically contracting muscle is increased. It has also been demonstrated by the injection studies of Spalteholz and Hochrein¹¹ that the myocardial capillaries are not compressed during muscular contraction and that cardiac systole should therefore in no way obstruct the coronary circulation. Finally, Rein¹² has shown on dogs with an intact circulation, that in the presence of a constant venous inflow, the coronary flow increases with an increase in the pulse rate, independently of the height of the aortic blood pressure.

It is beyond the scope of this paper to recapitulate the evidence offered in support of these contending observations, the validity of which must depend upon the accuracy of the methods employed. It was felt, however, that a clinical study of a group of cases with aortic valvular disease might give some indication as to the importance of a low diastolic pressure in the incidence of angina pectoris and from this aspect suggest to what extent the diastolic pressure influences the coronary blood flow. If angina should be found to occur with greater frequency among subjects with low diastolic pressures than among subjects with a similar type of lesion but in whom the blood pressure level in diastole is higher, it may be concluded that aortic regurgitation, per se, is a contributory factor to the production of angina pectoris and that the height of the diastolic pressure significantly influences the coronary blood flow. If no such proportionate relationship appears, however, it would seem that neither angina pectoris nor an insufficiency of the myocardial circulation can be explained on a basis of aortic regurgitation.

METHOD

The present investigation involves an examination of the case records of all patients with aortic valvular disease admitted to the Medical Service of the Krankenhaus St. Jacob, Leipzig, during the past two years. Attention was directed particularly to the incidence of angina pectoris in these subjects and to the height of their diastolic pressure levels.

For the purposes of this study it was essential to include a group of cases covering a wide range of diastolic pressures. In many sub-

jects, therefore, the diastolic level will be found to be well within the normal limits. All patients, however, exhibited definite lesions of the aortic valves. The diagnosis was made on a basis of a characteristic systolic or diastolic murmur at the aortic area, supplemented in the majority of cases by roentgenographic examination and confirmed in those cases on which autopsy was performed. The group was divided etiologically into cases of luetic and nonluetic origin. Only those cases having a positive Wassermann reaction were classified as luetic.* The nonluetic group included patients in whom the aortic valvular disease was due to arteriosclerosis or to endocarditis of rheumatic or bacterial origin.

Great care was necessary in the selection of blood pressure readings which represented an average mean of the variations recorded in individual cases in the course of observation. These variations in some subjects amounted to 30 mm. Hg in the diastolic pressure. In order that blood pressure readings should be comparable, determinations have been used, in the majority of cases, which were made in the Heart Station. These readings were taken under uniform conditions, usually within a few days of admission, with the patient reclining on a couch after a ten-minute rest period. Under the circumstances, patients in whom the diastolic pressure is within normal limits represent cases of aortic valvular disease which tend to have a relatively small amount of regurgitation (the actual index of regurgitation being, of course, dependent upon other factors such as the character of the pulse, the pulse pressure and the rate). They are included in the series for comparison with subjects having a similar pathological condition but a greater degree of aortic insufficiency and lower diastolic pressure levels.

An unquestionable diagnosis of angina pectoris was frequently difficult in a group of patients in whom subjective symptoms are so manifest. Only 16 per cent of the patients in the group were entirely free of cardiac sensations. The remainder complained of varying degrees of palpitation, precordial pain and indefinite sensations of cardiac distress. In many cases, angina pectoris was strikingly simulated. A diagnosis of angina was excluded, however, in all cases in which it could not be made with reasonable certainty. Only those patients were said to have angina who described the pain as having a steady, boring character, located over the upper part of the sternum or in the region of the left nipple. Extension of the pain to the left arm was not constant. It was associated with the characteristic feeling of intense anxiety in approximately one-third of the cases.

*It was recognized that some patients with consistently negative Wassermann reactions may have lues. All questionable cases, however, have been excluded from the luetic group because of the uncertainty of diagnosis and the necessity of satisfactorily explaining the pathogenesis of angina.

RESULTS

Etiology and Age.—Seventy-two patients with aortic valvular disease have been included in the series. Certain facts regarding etiology and age are of interest. Of the total group, 41 cases, or 57 per cent, were due to lues. The incidence of lues is somewhat higher than that reported by other writers¹³ probably because of the relatively less common occurrence of rheumatic infection in the locality from which these patients were drawn.¹⁴ Fig. 1 shows graphically the total percentage of subjects in each decade of life compared with the total percentage of subjects in each group in which the etiology was luetic. Before thirty years of age, only 7 per cent of the patients were luetic. With each decade, the incidence of lues increases until in the group over seventy

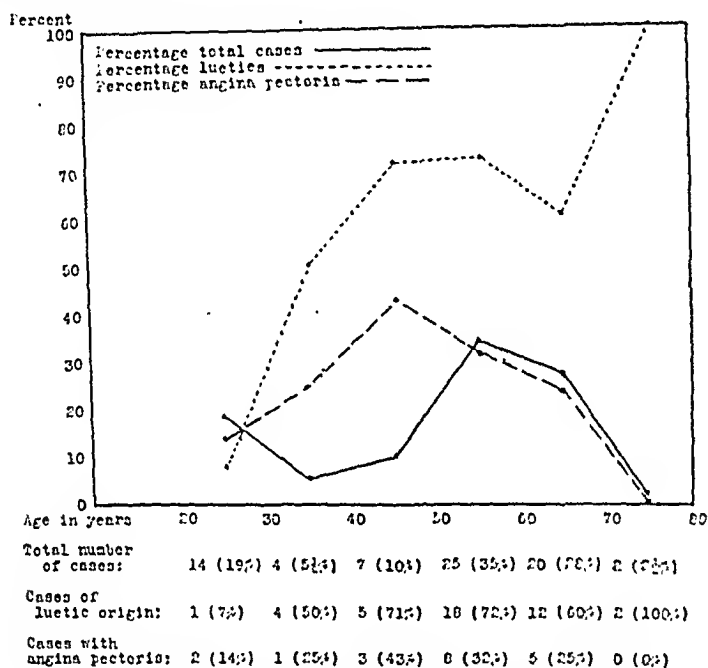


Fig. 1.—Total number of cases, incidence of luetic infection and incidence of angina pectoris in each decade of life.

years, no cases of nonluetic origin are found. This relationship is dependent upon the fact that luetic infection and the development of its cardiovascular manifestations occur at a relatively later period of life than in the case of rheumatic and bacterial types of endocarditis. A further inference from these figures may be drawn as to a relatively better prognosis of longevity in the presence of a luetic etiology. As compared with cases of rheumatic and bacterial endocarditis, this may, however, be more apparent than real, since the duration of life following the onset of valvulitis may be actually longer in nonluetic cases, although the average age of death in cardiovascular syphilis may be considerably later. The fact that no patients in the arteriosclerotic group were over seventy years old may possibly be due to the small number of patients in this group. On the other hand, it might be in-

terpreted as indicating that when the sclerotic process is sufficiently severe to cause such extensive involvement of the aortic valves, a concomitant sclerosis of the coronary vessels leads to a relatively early death. To what extent such factors are responsible can only be surmised. It can be stated with certainty only that in this series of cases, the patients with luetic valvulitis averaged a longer duration of life than did those of nonluetic origin.

Angina Pectoris.—The percentage incidence of angina pectoris is also charted in Fig. 1. This syndrome was present in two of the fourteen patients under thirty years of age. Both cases were of rheumatic origin. Angina is uncommon before middle life, but in young people it is almost always associated with aortic insufficiency.¹ The maximum incidence of angina pectoris in this series occurred in the fourth and fifth decades, thereafter declining rapidly. No cases occurred in the group over seventy years old. Since angina associated with aortic valvular disease usually results from obstruction of the coronary ostia, thus involving an interference with the blood supply to a relatively large area of the myocardium, its appearance, under the circumstances, may be assumed to be a particularly bad prognostic sign.

Congestive Failure.—Angina pectoris usually disappears with the onset of congestive failure. It was important, therefore, for the validity of any conclusions as to the relationship of the incidence of angina to the height of the diastolic pressure to determine to what extent this phenomenon is increased in the presence of low diastolic levels. It was found impractical to estimate the degree of failure for each individual case of this series. The patients were therefore grouped on a basis of whether or not any evidence of congestion was present, simple enlargement of the liver being considered the earliest sign. As might be anticipated, the highest percentage of circulatory failure occurred in the group with the lowest diastolic pressures. Eight patients, or 66.6 per cent, of the group with diastolic pressures below 40 mm. Hg showed evidence of congestion. Between 40 and 79 mm. Hg, 19 patients, or 60.4 per cent, had congestion; while above 80 mm. Hg, congestion was present in 5 patients, or 41.6 per cent. The incidence of this phenomenon is therefore least marked among the subjects with normal diastolic pressures. On the other hand, it is significant that between the group with moderately low diastolic levels and the group in which the pressure in diastole was below 40 mm. Hg, only a negligible difference of approximately 6 per cent in the incidence of circulatory failure was apparent. The level of the diastolic pressure does not therefore seem to be an important cause of circulatory congestion. A factor, evidently of much greater importance, is the degree of the associated damage to the myocardium. The fact that this may be to some extent

proportional to the degree of valvular damage may explain the slight increase in the incidence of congestion in the presence of marked regurgitation.

Subjective Symptoms.—As previously remarked, subjective manifestations are particularly conspicuous in the symptomatology of aortic insufficiency and seem to depend, in part at least, upon the high pulse pressure incident to regurgitation and to the increased velocity of systolic ejection. The physical activity of the patient is unquestionably limited in proportion to the severity of these symptoms. Limitation of physical activity has been suggested as an explanation of the disappearance of angina pectoris with the onset of congestive failure. The same might be said of severe subjective symptoms. The relative incidence of these manifestations has therefore been determined in the present series. Subjects with aortic valvular disease complain usually of severe palpitation and ill-defined sensations of cardiac distress. Precordial pain is often present and differs from the pain of angina pectoris chiefly in its location and in its intermittent, stabbing, rather than steady, boring character. Such manifestations, in varying degrees of severity, were present in 82 per cent of the total group. They occurred in 10 subjects, or 83.4 per cent, of the patients with diastolic levels below 40 mm. Hg, 40 subjects, or 83.4 per cent, of the group with diastolic pressures between 40 and 79 mm. Hg and in 9 subjects, or 75 per cent of the group with diastolic pressures of 80 mm. Hg or above. Thus it is apparent that although palpitation and precordial distress are somewhat less marked among subjects with normal diastolic pressures, the difference is really negligible and does not appear to increase in proportion to a lowering of the arterial pressure in diastole.

Relationship of Angina Pectoris to the Diastolic Pressure.—Of the 72 cases of aortic valvular disease included in this series, 19 subjects, or 26.4 per cent, had angina pectoris. The syndrome varied in type and severity between individuals. In some cases it appeared as a relatively mild angina of effort, in others it occurred in severe spontaneous attacks. In all cases, however, the symptoms were characteristic. Fig. 2 presents the cases divided into three groups according to the height of the diastolic pressure. The total percentage of patients in each group is compared graphically with the percentage of patients in that group having angina. From this it will be seen that of the subjects with diastolic pressures below 40 mm. Hg there were 2 cases, or 16.7 per cent, of the group with a diagnosis of angina pectoris, between 40 and 79 mm. Hg, 16 cases, or 33.3 per cent, and above 80 mm. Hg, one case, or 8.5 per cent. It is evident from these figures that the incidence of angina pectoris does not increase in proportion to a diminution in the diastolic pressure level. Angina is somewhat less frequent in the subjects with the highest diastolic pressures than among those with diastolic levels below 40 mm. Hg. The greatest incidence is found, how-

ever, not at the lowest diastolic levels, as should be the case were low diastolic pressures influential in the production of angina, but in the intermediate group with diastolic levels between 40 and 80 mm. Hg. The presence of a marked degree of aortic regurgitation usually indicates a more extensive pathological condition than is likely to be found in cases in which less significant insufficiency of the valve occurs. It is easy to understand, therefore, why the percentage of angina pectoris is higher among cases in which aortic regurgitation is present (as far as can be judged by the diastolic pressure) than in cases in which the absence of significant regurgitation indicates that the disease process has not been severe enough to disturb the valvular

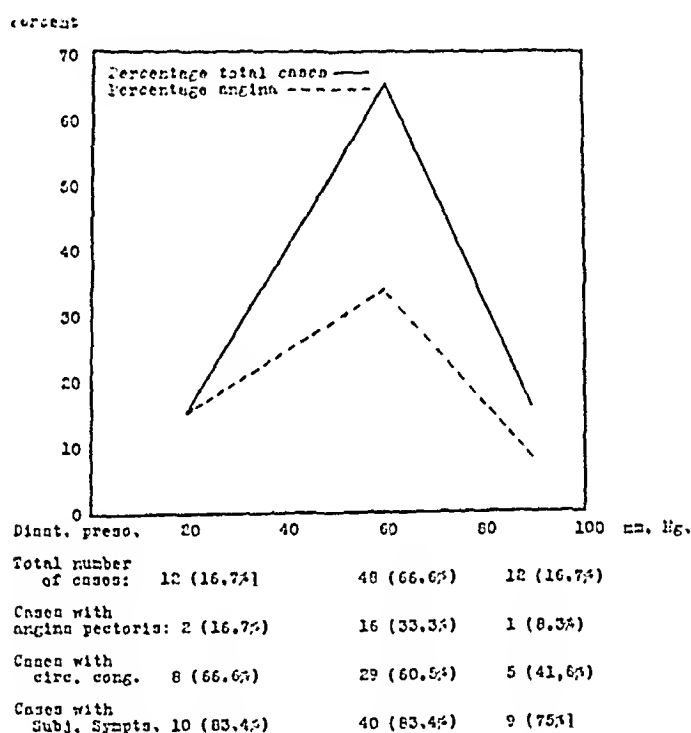


Fig. 2.—Total number of cases and the incidence of angina pectoris, circulatory congestion and cardiac subjective symptoms grouped according to the height of the diastolic pressure.

function. On the other hand, the fact that increasing degrees of insufficiency appear to cause no corresponding increase in the incidence of anginal manifestations indicates that the diastolic pressure level must be of relatively slight importance in determining the extent of the coronary blood flow.

PATHOGENESIS OF ANGINA PECTORIS IN AORTIC VALVULAR DISEASE

The conclusion that angina pectoris cannot be dependent upon a low diastolic pressure receives support if it can be shown that all cases of angina associated with aortic valvular disease can be explained on other pathogenic bases. A vast amount of experimental evidence, which it is unnecessary here to recapitulate, indicates that anginal pain is a

manifestation of myocardial ischemia. On the other hand, the chemical mechanism by which the pain stimulus is produced, the apparent variations in the sensitivity of different subjects to angina, why pain fails to appear in many cases of obvious coronary obstruction and whether vasomotor disturbances of the coronary vessels actually do occur to the extent of producing angina pectoris are points which have not yet been clearly demonstrated. In the present state of our knowledge, therefore, the occurrence of angina is sufficiently explained for the purposes of this investigation if the presence of factors tending to diminish significantly the coronary blood flow, either locally or throughout the myocardium, can be shown.

The pathogenesis of angina in the luetic subjects of this series can be explained in the majority of cases by a stenosis of the coronary ostia which is a usual accompaniment of specific aortitis. Other cases may be explained as being due to loss of elasticity of the aortic wall, as Hochrein¹⁵ has shown that a proportional diminution of the coronary blood flow is associated with this type of pathological condition. Other factors such as coronary sclerosis may, of course, be supplementary. Five of the 19 cases of angina, however, did not have lues and in these the significance of the pain must be otherwise interpreted.

Two of the 5 cases were unquestionably due to coronary sclerosis. Post-mortem examination was performed in one of these and demonstrated widespread calcification of the coronary vessels with complete occlusion of the descending branch of the left coronary artery. The other subject was a male of sixty-seven years showing marked sclerosis of the peripheral vessels. The heart was dilated and there was evidence of adhesive pericarditis. The arterial pressure was 110/70 mm. Hg, so that in any case angina could not be accounted for by a low diastolic pressure.

Two subjects, both males, aged twenty-nine and fifty-eight years, had a history of recurrent attacks of rheumatic fever. Physical examination showed insufficiency of the aortic valves while an apical diastolic murmur indicated that the mitral valves were also involved in the rheumatic process. In both cases, angina pectoris was of the effort type, the pain appearing usually on physical exertion and passing off with rest. Angina pectoris is said to be a relatively unusual complication of mitral stenosis.^{16, 17, 18} When this combination does appear, post-mortem examination may fail to reveal any apparent cause for the pain¹⁹ which may be dependent upon a functional stenosis of the coronary ostia.²⁰

The fifth subject was a male, aged twenty-seven years. He had a history of recurrent attacks of rheumatic fever, and physical examination indicated an involvement of the aortic and mitral valves. The blood pressure at rest was 150/40 mm. Hg. Attacks of angina were of the spontaneous type. Angina in this case also may have been due

to mitral stenosis. On the other hand, it may be of the type described by Lewis²¹ in which angina appears in spontaneous attacks associated with high blood pressure. This syndrome is said to occur frequently in relatively young subjects with free aortic regurgitation. Lewis explained the attacks as being due to a generalized vasomotor disturbance wherein the coronary vessels are so involved that a relative myocardial ischemia is produced. That the attacks are vasomotor in origin is supported by the fact that the pain yields promptly to the administration of nitrites. The patient described above appears very comparable to those discussed by Lewis. He was a tobaccoist by occupation and smoked to excess, facts which support the probability of a vasomotor pathogenesis. While no blood pressure readings during the attack are available, the high resting systolic level is suggestive, and the attacks themselves were essentially similar to those of Lewis' subjects.

Thus it appears possible to explain the pathogenesis of all cases of angina pectoris associated with aortic valvular disease without predicating the influence of a low diastolic pressure. Such explanations must be made, however, with the reservation that our understanding of this syndrome is still very incomplete and that forthcoming work may demonstrate the fallacy of many of our present accepted views. But whatever may be the actual cause of anginal pain, it seems very unlikely that a low diastolic pressure plays any conspicuous rôle in its production.

DISCUSSION

The evidence presented as to the relationship of angina pectoris to aortic valvular disease does not appear to be open to serious criticism. In regard to the particular group of subjects studied, in-patients were selected rather than ambulatory cases because in the majority of instances better opportunity had been afforded for thorough investigation and diagnosis. In-patients, furthermore, have had their aortic disease longer as a rule and are therefore more likely to have developed angina than when first seen as out-patients, so that the maximum incidence of angina should be found in such a group.

Factors mitigating the reliability of the figures obtained appear to be chiefly the relatively small number of patients with very low diastolic pressures and the possible influence of congestive failure. A large series of cases is, of course, always preferable. On the other hand, the conclusions would have been as adequately demonstrated if the percentage incidence of angina pectoris had been the same at all diastolic levels while actually it was diminished at low pressures. For this reason it is improbable that chance errors have significantly altered the ultimate conclusions.

That congestive failure or subjective symptoms play little or no part in diminishing the relative incidence of angina is clear from the pre-

ceeding observations on these phenomena. The increase in the percentage of patients with low diastolic pressures who showed evidence of circulatory congestion is, in this study, not sufficient to explain the relatively greater decrease in the incidence of angina in the same group. A much more likely interpretation is the probability that if the mean arterial pressure falls to the extent of producing any physiological disturbance, peripheral congestive failure supervenes before the onset of angina. This explanation complements the view that the blood flow through the coronary vessels is modified principally by the work of the heart rather than by variations in the aortic perfusion pressure. Under the circumstances, the coronary circulation would be less affected than would those parts of the circulation which are more dependent upon the arterial pressure. An angina due to insufficiency of the aortic perfusion pressure would therefore not appear until after the occurrence of congestion in the periphery. Congestive failure is not dependent upon valvular competence but rather upon the relative efficiency of the myocardium. Thus even in the presence of a very low diastolic pressure in the aorta, the effective perfusion pressure of the coronary and systemic vessels remains sufficient as long as the myocardium is competent. When the myocardium fails, peripheral congestion appears and angina pectoris does not occur.

The physiological application of these observations lies in the fact that they agree with the conclusions of Hochrein and his coworkers that alterations in coronary blood flow are dependent chiefly upon the work of the heart rather than upon variations in the aortic perfusion pressure and that a low pressure in diastole does not significantly affect the coronary circulation. By the same token, they support the view that cardiac systole does not obstruct the myocardial blood flow. Of clinical importance is their significance in regard to the appearance of angina pectoris in cases of aortic valvular disease. Angina cannot, under the circumstances, be attributed to the low diastolic pressure of valvular insufficiency. Its presence indicates a diminution of the coronary blood flow due to other complicating factors. Of these, aortic valvular disease itself frequently involves blockage of the coronary ostia or loss of elasticity of the aortic wall. Less often is the angina dependent upon purely concomitant factors such as mitral stenosis, vasomotor spasm or coronary sclerosis.

SUMMARY AND CONCLUSIONS

An analysis is made of 72 cases of aortic valvular disease with special reference to the relationship between the incidence of angina pectoris and the height of the diastolic pressures. Etiology and age are discussed.

Angina pectoris occurred in 8.3 per cent of the cases in which the diastolic pressure was 80 mm. Hg or above, 33.3 per cent of the cases

in which it was between 79 and 40 mm. Hg, and in 16.7 per cent of the cases in which it was below 40 mm. Hg. The fact that this syndrome did not occur most frequently in the latter group indicates that a low diastolic pressure is of relatively slight importance in the pathogenesis of angina pectoris. The incidence of congestive failure was also studied, but its increase at low diastolic levels was insufficient to account for the relatively greater decrease in the incidence of angina in the same group.

These observations indicate that the appearance of angina pectoris in cases of aortic regurgitation cannot be attributed to an insufficiency of the coronary perfusion pressure during diastole. They support the view of Hochrein that the work of the heart is the most important factor in determining the volume of the coronary blood flow, that the myocardial circulation is relatively little affected by alterations in the diastolic pressure level and that cardiac systole does not significantly obstruct the coronary vessels.

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THE PROGNOSIS IN GONOCOCCAL ENDOCARDITIS⁶

REVIEW OF LITERATURE AND REPORT OF CASE WITH SPONTANEOUS RECOVERY

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THE writings of Ricord¹ in his classical treatise on venereal disease were probably the first demonstration of the fact that gonorrheal infection may go to systemic distribution with visceral involvement. It is this work that indicated clearly that gonococcus infection may involve the heart. The first clinical demonstration of gonococcal heart disease was that of Brandes,² whose paper seemed to demonstrate clearly that there was a connection between the onset with an acute urethritis and the cardiac involvement. If the clinical observations of Brandes are indubitable, his is probably the first recorded case of gonococcal endocarditis with recovery. At this point, it may be said, that early writers recognized that gonococcal endocarditis may follow urethritis without the appearance of arthritis.³⁻⁵ Lucas⁶ found arthritis absent in fifteen cases out of forty-three. The first recorded recovery of the gonococcus from the circulating blood was probably that of Rothmund,¹⁰ and elaborated on more fully by Souplet.¹¹ Hewes¹² soon followed thereafter with reports of positive blood cultures in gonorrheal polyarthritis. The first demonstration of gonococci in the valves in cases of gonococcal endocarditis was that of Rendu and Halle.¹³ In the German literature, an early report concerning gonococcal endocarditis was by Shedler,¹⁴ which is of particular interest because it treated of a fatal case with complete post-mortem findings. Desnos¹⁵ demonstrated specimens with endocarditic involvement as early as 1877. These specimens were from a man who developed arthritis as a sequel to a urethritis, and in the midst of a severe febrile course an endocarditis was found to be present. Polypoid vegetations of a characteristic variety were found on the mitral and aortic cusps. In Shedler's case, the presence of nephritis was emphasized; of unusual interest in the light of the fact that clinical studies of gonococcal endocarditis in recent years (Thayer, etc.) have revealed not a few cases with renal involvement, some with actual termination in uremia. The report of Delprat¹⁶ included two cases, one with recovery; this case having developed loud cardiac murmurs a few days after the cessation of a thick urethral discharge, the patient having been discharged with severe endocardial involvement. Morel¹⁷ described a case in which healing took place; in this instance

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on the third day of a febrile period, the hitherto rich urethral discharge diminished, at which time a loud apical systolic murmur was found to be present for the first time. Subsequently there set in an arthritis of the left knee joint and fourteen days after, amid chills and fever, a diastolic murmur appeared at the base of the heart with the coincidental appearance of severe dyspnea. The patient died six weeks after the onset. An early instance where the organisms were found post mortem on section but not ante mortem in the circulating blood is recorded by Wilms.¹⁸ It was this author's belief that the organisms found in the valves were pyogenic bacteria which entered the circulation after involving the urethra as secondary invaders. The organisms found on the heart valves were described as intracellular diplococci for which reason the theory of secondary pyogenic invasion is doubtful. The report of Loeb¹⁹ is interesting because it considers the pleuropulmonary complications among the other visceral manifestations of gonorrhea; a subject which in recent years has been reconsidered by Pratsieas.²⁰ The latter writer describes a case with systemic infection in which a pleural effusion developed from which organisms were recovered having the morphological characteristics of gonococci. This patient had no endocardial involvement clinically demonstrable. The offending organisms could not be identified culturally because they failed to survive on subculture. Bressel²¹ described a case of gonococcal bronchopneumonia in which the gonococci were recovered in the sputum. Similar reports were made by Wynn,²² Scherrer,²³ Barbiani²⁴ and Ahman.²⁵

Lenhartz²⁶ in his classical work expressed the opinion that recoveries in gonococcal endocarditis sometimes do occur. He quotes the case of a sixteen-year-old girl who eight weeks before coming under his observation had had an acute gonorrhea. Four days before admission dyspnea, precordial oppression and severe constitutional symptoms set in. The urethritis and endocervicitis were severe, and smears taken locally were positive for gonococci. Unusually loud systolic and diastolic murmurs were heard at the base which subsequently completely and permanently disappeared. During the acute febrile course there were two chills, high intermittent fever and practically no local evidence of disease. Blood cultures were not reported. The absence of local disease (urethritis, etc.) is a fact that has been particularly emphasized also in recent years. Lenhartz judiciously laid stress on the difficulty of interpreting clinical findings because he felt certain that systemic gonococcal infection could readily occur in people with old rheumatic valvular disease; for which reason he cautioned against the indiscriminate assignment of a gonococcal etiology in these cases. Karsner²⁷ recently made the statement that in order to establish the diagnosis of gonococcal endocarditis the presence of gonococci in the blood or the lesions must be shown. This attitude contrasts sharply with that of Jagie and Schiffner,²⁸ who within fairly recent years expressed the

opinion that mild cases of gonococcal sepsis occur with endocardial involvement which not infrequently go on to complete recovery. These writers believe that if there is no other etiological factor for cardiac disease and cardiac involvement occurs in the course of a full-blown gonococcal infection, the diagnosis of gonorrheal heart disease is warranted. They feel that in the verrucose form of gonococcal endocarditis as contrasted with the ulcerative form, cases frequently go on to a termination with complete recovery, but in most cases a valvular defect remains. They also are of the opinion that the verrucose form of endocarditis is not so infrequent as the ulcerative form. They cite the case of a thirty-eight-year-old male who following an acute urethritis developed a complicating epididymitis. Three weeks thereafter during an acute febrile period a blowing systolic murmur was heard at the apex, and in yet another three weeks the left ventricular border was found to be displaced to the left. The systolic murmur increased in intensity. On discharge, the heart showed outspoken cardiac enlargement with a heaving apical impulse, a loud systolic murmur at the apex and an accentuation of the second pulmonic sound.

Concerning the general subject of gonococcal endocarditis, the literature abounds in descriptions of the clinical course, bacteriological and pathological findings in this disease. In the last decade and a half, over one hundred reports have appeared on the subject. The German literature emphasizes particularly the pathological aspects of the disease; the French, the bacteriological; the American, the clinico-pathological. Of the almost innumerable reports of fatal cases, there may be mentioned those of Vander Veer,²⁹ Lefebure,³⁰ Edwards,³¹ McCants,³² Lion and Levy-Bruhl,³³ Dwyer,³⁴ Riecker,³⁵ Johnston and Johnston,³⁶ Gill,³⁷ Klein,³⁸ Warfield,³⁹ Bard, Langernon and Gardere,⁴⁰ Gallavardin,⁴¹ Lartigan,⁴² Villela and Torres,⁴³ Smith,⁴⁴ Galois,⁴⁵ Barbe and Meynet,⁴⁶ Brebner,⁴⁷ Kramer and Smith⁴⁸; and more recently there have appeared the reports of Kirkland,⁴⁹ Cooper and Klinek,⁵⁰ and Hoffman and Taggart.⁵¹ The attitude of these writers concerning the prognosis in gonococcal endocarditis varies widely. Thayer,⁵² whose monograph on this subject will remain one of the classic reviews of the disease, is of the opinion that recoveries do occur in gonococcal endocarditis, but are probably extremely rare. Warfield in his report expresses the belief that no true cases of gonococcal endocarditis recover. Libman⁵³ makes the statement that while all cases of acute bacterial endocarditis are said to be fatal without exception, the impression he had gained was that acute gonococcal endocarditis seemed to carry the best prognosis.

A survey of the early literature on the subject of recoveries in cases of gonococcal endocarditis, reveals that the first recorded case is that of Brandes, as has already been mentioned. The writings of the pre-bacteriological days are from time to time involved in the reports of

such cases; viz., Delprat,¹⁶ and Morel.¹⁷ The report of Lenhartz²⁶ cited previously represented clearly a recovered case. The only source of possible doubt was the failure to recover the gonococci from the circulating blood. The clinical course was typical from every point of view except for the fact that no embolic lesions appeared at any time. Gourvich⁵⁴ in his report of a recovered case reviewed the cases of recovery to that time. He failed, however, to distinguish between hemic murmurs that arise in the course of an acute febrile disease and the organic murmurs of true gonococcal endocarditis. Thayer⁵² in this connection remarks very properly that early endocarditis is often difficult to recognize, as is the case in rheumatic fever, and just what relationship there is between murmurs heard during an acute gonococcal infection and preceding chronic valvular disease is often impossible to say. Unger⁵⁵ cited a case of an eighteen-year-old boy who developed a fresh endocarditis with an apical systolic murmur and functional insufficiency. He ran an irregular fever, developed arthritis and eventually recovered. Blood culture during the acute phase of his illness was positive. The classic case of Silvestrini⁵⁶ is worthy of review in detail. This case probably represents the first record of systemic gonococcal infection with blood stream invasion, polyarthritis, endocarditis and jaundice. The patient was a male of twenty-nine years, who one month before his admission had contracted a gonococcal urethritis. Twenty days after the cessation of the urethral discharge, he was taken with malaise, chills and fever. Three days later an acute polyarthritis set in involving the wrists and metacarpophalangeal joints. Seven days after the onset of the fever, icterus of the skin and mucous membranes appeared. The urine showed the presence of bile but no albumin or sugar. On the thorax there appeared several erythematous hemorrhagic blebs. The liver and spleen were enlarged. A systolic murmur was heard at the apex of the heart, transmitted to the axilla. Subsequently, involvement of the ankles, wrists and knees set in. Upon the day after admission, a pericardial rub was heard; jaundice became deeper, the liver larger. After an illness of three months' duration the patient recovered and was discharged with ankylosis and stiffness of the joints and a full-blown mitral insufficiency. Blood cultures done on enriched media, viz., glucose serum and pleural fluid, grew out the gonococci. Smears of a milky fluid obtained from one of the involved joints showed leucocytes within which were numerous gram negative diplococci. An opinion as to whether this represents a truly recovered case of gonococcal endocarditis must be held in abeyance; the failure to report changes in character of the cardiac lesions makes one suspect that the writer was more probably dealing with a case of gonococcal sepsis with icterus than with one of true gonococcal endocarditis. Withington⁵⁷ cited the case of a thirty-six-year-old male with a urethritis of one and a half months' duration who developed an acute aortic

endocarditis which was found to be present on admission. He ran a febrile course with chills and fever, but no arthritis was present. Blood cultures revealed the presence of gonococci. This patient went on to complete recovery with no signs other than the persistence of a systolic murmur at the base of the heart in the second left interspace. During the acute febrile period, precordial pain, orthopnea, cardiac enlargement, pericardial friction rub and gallop rhythm had been present. Dieulafoy⁵⁸ described a case of recovered gonococcal endocarditis in which the differential diagnosis from typhoid fever became a problem. The patient was a male of twenty-three years whose illness had an acute onset with high remittent fever. Urethritis was present one month before admission. Sweating, headache and diarrhea were present after the onset. Because of the profuse diaphoresis, the diagnosis of typhoid fever was questioned. There was no arthralgia present at any time. Two days after the patient was first seen, a mitral murmur was heard of a scraping musical quality, for which reason it was supposed that an ulcerating endocarditis was present. Hemorrhagic papular skin lesions occurred on the abdomen, thorax and thighs. There was a severe secondary anemia associated with a leucocytosis and polynucleosis. The urethral smears showed the presence of gonococci. The blood culture likewise was positive for gonococci. The patient was treated with gonococcus vaccine, and despite the occurrence of a complicating bronchopneumonia, recovery took place in forty days after onset. The patient was left with a permanent mitral lesion. Faure-Beaulieu⁵⁹ reviewed thirty-four cases of gonococcal sepsis in an excellent monograph on this subject. Of these patients, ten died. Of the twenty-four recovered cases, in three, apparently definite endocardial involvement was present. Undoubtedly prompted by the reported success of vaccine therapy in this disease, as well as with the use of anti-gonococcal serum, Schiele and Dorbeck⁶⁰ used an antiserum in a case of severe gonococcal sepsis in which an acute endocarditis was said to have been present. In one month the fever subsided in their case and the cardiac signs disappeared. Sagot⁶¹ quotes the case of Marfan and Debie as illustrating the occurrence of gonococcal endocarditis with recovery. A ten-year-old girl was seen with a week's history of abdominal pain and gave a typical typhoidal appearance. There was marked abdominal distention, but no vomiting or diarrhea. The diagnosis of pelvic peritonitis was made. A vaginal discharge revealed, however, the presence of gonococci. The heart was found to be slightly enlarged to the left in the fifth interspace just outside the nipple line. There was also slight cardiac enlargement to the right. A systolic thrill was present at the apex as was an intense rough systolic murmur which was transmitted to the axilla. A mitral endocarditis was thought to be present, and in view of an entirely negative past history, the cardiac lesion was presumed to be a recent one. Two days after admission

a mesodiastolic murmur was heard. The blood culture revealed the presence of the gonococcus. The patient was given in addition to local therapy for the vaginitis, gonococcus vaccine. She recovered three weeks later, with signs of a mitral valvulitis and adherent pericardium. These signs were found to be present on examination ten months after the onset. Luithlen⁶² reported a case of a twenty-six-year-old male taken with acute posterior gonococcal urethritis. One month afterward, during which time the urethritis was being treated, he complained of cardiac pain. Cardiac findings at this time were a soft systolic murmur at the apex, slight cardiac enlargement to the left and a bradycardia. The next day the patient went into cardiac collapse; he then became slightly febrile and the spleen became just palpable. Temperature became normal five days after this episode. He eventually recovered. The author of this report feels that this represents a case of recovered gonococcal endocarditis. More recently, Aubertin and Gambillard,⁶³ citing the successful use of anti-gonococcus serum at the hands of Sehiele and Dorbeek, previously quoted, undertook the use of this form of therapy in the treatment of a case of gonococcal endocarditis that came under their care. An eighteen-year-old male came under their observation following the onset of an illness ushered in with a shaking chill. The less immediate illness dated back to the onset with an acute urethritis which the patient treated with self-medication. Nine months later, arthralgias, unassociated with fever set in, for which five injections of gonococcus vaccine were given. At the time marked pallor of the skin and mucous membranes was noted. Two months thereafter, a systolic murmur was discerned at the base of the heart, and a leucocytosis and polynucleosis were found to be present. Two days after the systolic murmur was discovered, a diastolic murmur at the base of the heart was heard. At no time was there a Corrigan pulse present. The spleen was not palpable; the urine was negative. After one month of a severe febrile course, anti-gonococcal serum was administered, in all eight injections of 40 c.c. were given. This was followed in due time by a severe serum sickness, characterized by arthralgias and urticaria, following which the patient became afebrile. During the course of this severe febrile illness, six blood cultures were taken, all of which showed no growth. It is obvious from a review of this case, that the writers were not dealing with a case in which endocarditis was definitely present. The time of onset with systemic symptoms post dates the onset with acute urethritis by a period of time which exceeds by many months the usual period when endocarditic involvement takes place. The absence of embolic phenomena, palpable spleen and positive blood culture tends to support the view that an actual gonococcal endocarditis was not present in this case. Schottmüller⁶⁴ in his treatise on sepsis expresses the feeling that one

must be cautious before giving an absolutely hopeless prognosis in gonococcal endocarditis. He cites recovery in a case he himself saw in addition to a case reported by Joehmann. Lesehke⁶⁵ reported a recovered case in which we find that the critical drop in temperature occurred following a febrile episode during which the temperature was the highest that it had been at any time during the illness. In the case that I shall quote as a recovered case of gonococcal endocarditis, the same phenomenon occurred. Some writers invoke the theory of extreme thermolability of the gonococcus as a cause of self-sterilization, so to speak. It is, to be sure, a subject of much speculation, and one with which I shall not attempt to cope. Prendergast⁶⁶ remarks on the general character of gonococcal endocarditis by saying that it does not differ essentially from other forms of acute bacterial endocarditis, except that the outlook for life is better. Of two cases known to that writer, one recovered. He feels also that if an acute endocarditis occurs in a patient with gonorrhea and no organisms can be recovered, because of the well-known difficulty in culturing the gonococcus, the presumption is that a gonococcal endocarditis is present. The recovered case he cites is that of a man of twenty-four years whose illness began with a urethral discharge, followed in one month with epididymitis. About six weeks later he complained of pains in the extremities and precordia, at which time the heart was normal in size and no murmurs were heard. Two days later there was increasing fever, sweating and prostration. The heart was enlarged, and long soft mitral systolic and short aortic diastolic murmurs were heard, followed in two days by a pericardial rub. Sixteen days after onset of precordial pain a pericardial effusion was present, and in one month the effusion was gone. The patient approached normal but the murmurs remained. He was seen five months later and a faint aortic diastolic murmur was heard, there was a large pulse pressure present, but he was otherwise normal.

Within the last two years there have appeared two reports of unusual interest in connection with the surgical therapy of gonococcal bacteremia in women, by the radical extirpation of diseased foci in the pelvis. The earlier report of Wheeler and Cornell⁶⁷ concerns the recovery of a nineteen-year-old female who had an intermittent bacteremia of pelvic origin, from whose blood stream the gonococci disappeared following radical extirpation of the diseased foci in the pelvis. Gonococcal endocarditis was not definitely established in this case. Encouraged by this result and feeling that gonococcal endocarditis carried with it such a bad prognosis, Garlock⁶⁸ described a similar case with a successful surgical result. A female of twenty-six years came under his observation with fever and a rash of four weeks' duration. The onset was with a chill which had recurred one week thereafter. Pain and stiffness in the ankles set in; there was no previous history

of rheumatic fever or chorea, nor of gonorrheal infection. The heart was found to be slightly enlarged to the left, and a soft systolic murmur was heard at the apex and a rough systolic murmur at the pulmonic area. The spleen was not felt. The skin of the back and of the front of the chest was covered by a macular rash. Pelvic examination showed only a boggy uterus. The urine was negative; there was no anemia; a leucocytosis was present. The blood cultures grew out the gonococcus on three occasions, and the cervical smears also showed the presence of the gonococcus. The heart became enlarged under observation, and systolic and diastolic murmurs were heard at the apex. Anemia then ensued. The diagnosis of gonococcal endocarditis was made, and since it was felt that the prognosis was hopeless, salpingohysterectomy was performed. The patient's temperature promptly fell to normal, and she was discharged after seven weeks, all blood cultures during this time being sterile. The patient was seen six months later, and no pathological changes could be discovered in the heart. This patient had also had the benefit of five transfusions during the course of her treatment. The value of repeated transfusion in the treatment of gonococcal endocarditis is the subject of a paper, by Perry,⁶⁹ dealing with a recovered case. A male of twenty-two years first came under his observation with a complaint of fever of one week's duration. The patient had had a urethral discharge for the three months previous to the onset of the acute illness. He had been through an insurance examination the year before, and no cardiac murmurs were noted. One week after he was first seen he had a chill and a rise of temperature to 105°. The heart revealed in addition to a tachycardia, a slight enlargement to the left. At the pulmonic area a soft low-pitched murmur was heard, systolic in time. A few days later a diastolic murmur appeared at the pulmonic area. Blood culture grew out the gonococcus. The patient was given repeated small transfusions, went through several episodes of pulmonary embolism, recovered and was discharged well after four months. In all, fourteen transfusions were given, and one injection of convalescent serum was given. The patient was seen one and a half years later. The author of the report informs me⁷⁰ that the patient is clinically well and has a definite pulmonary insufficiency which is causing him no symptoms. In this connection it is interesting to note that in the paper of Libman previously cited⁵³ a case of gonococcal endocarditis involving the pulmonary valve which went on to spontaneous recovery seen by Doctor Edward Janeway, was mentioned.

At the Mount Sinai Hospital, New York City, up to the present date there have been seven cases of gonococcal endocarditis. In all of these except the case described there was a fatal issue. Because of the rarity of recovery in this disease and the remarkable clinical course, the following case is reported:

REPORT OF CASE

E. S. Acc. No. 334293, Aged nineteen years, an unmarried stenographer, entered on the First Medical Service of Doctor Leo Kessel, The Mount Sinai Hospital, on January 15, 1932. She was discharged well on February 27, 1932. She was an American born girl who with the exception of a five months' stay in Florida, during 1930, had always lived in New York City. She denied ever having had pneumonia, typhoid fever, scarlet fever, diphtheria, chorea, frequent sore throats, "heart trouble," or rheumatic fever. At the age of ten years, a tonsillectomy had been performed. Her menses commenced at twelve years, were always regular and lasted four days. Her last menstrual period had occurred in December, 1931. She had missed three periods during her pregnancy (see present illness). Her present illness began three months before admission, when, in an attempt to terminate a pregnancy of four months' duration which was associated with morning nausea and amenorrhea, she went to a midwife who inserted a heavy gauze pad into the vagina. This, the patient removed twenty-four hours later with a small blood clot. This was accompanied by severe lower abdominal pain of a cramplike character, followed twenty-four hours later by a steady severe knifelike pain in the right lower quadrant which was increased by coughing and breathing, and unaffected by urination or defecation, which two functions were normal. There was no nausea or vomiting. The temperature rose to 104° and returned to normal the following day. She was up and about for one week when the lower abdominal pain returned this time more severe on the left side. At this time the patient had a curettage of the uterus performed. Pain remained persistent for the two months thereafter and was accompanied by daily rises of temperature to 105° , associated with profuse sweats. There had been no vaginal discharge except for a foul bloody one, one week after the clot was passed at the onset. There was no epistaxis, no respiratory symptoms, no tender finger tips or toes. Six days before admission she had received a 500 c.c. transfusion. Physical examination on admission revealed a chronically ill, underdeveloped female with marked pallor of the skin and mucous membranes. The skin of the entire body was slightly of a café-au-lait hue. No petechial spots were seen anywhere on the skin or mucous membranes and no splinter hemorrhages under the finger nails. The pupils were round, regular and reacted to light and accommodation. The sclerae were not icteric. The fundi were normal. The teeth were in poor condition, and the tongue was coated; there was slight fetor oris. The pharynx was slightly red; the tonsils were cryptic. There was no lymphadenopathy. The lungs were negative. The heart was not enlarged to the right or to the left. There was no increase of cardiac dullness over the pulmonary conus. The apex impulse was forceful. There were no murmurs heard. A_2 was greater than P_2 . The rhythm was regular. The spleen was felt two and a half fingers below the subcostal margin; the edge was firm. No perisplenic friction rub was heard. The liver edge was felt one finger breadth below the right subcostal margin. On pelvic examination, the cervix was found to be slightly patulous and eroded. A slight mucoid discharge issued from the os uteri; the findings were otherwise negative.

Laboratory Data: Hemoglobin 62 per cent, R.B.C. 4,550,000; W.B.C. 5,400, Polys. 83 per cent, of which 9 per cent were staff cells. There was marked toxic granulation of the polynuclears. Platelets 250,000. B.P. 108/70 mm. Wassermann and Kahn tests, negative. Blood urea nitrogen 11 mg. Sedimentation time forty minutes. Tourniquet test negative. Cervical smear for gonococci negative. Urine on admission was acid in reaction, contained one plus albumin, no sugar, and 2-5 R.B.C. per high power field, and numerous W.B.C., hyaline and granular casts were seen microscopically. Urine concentration test 1.006-1.014.

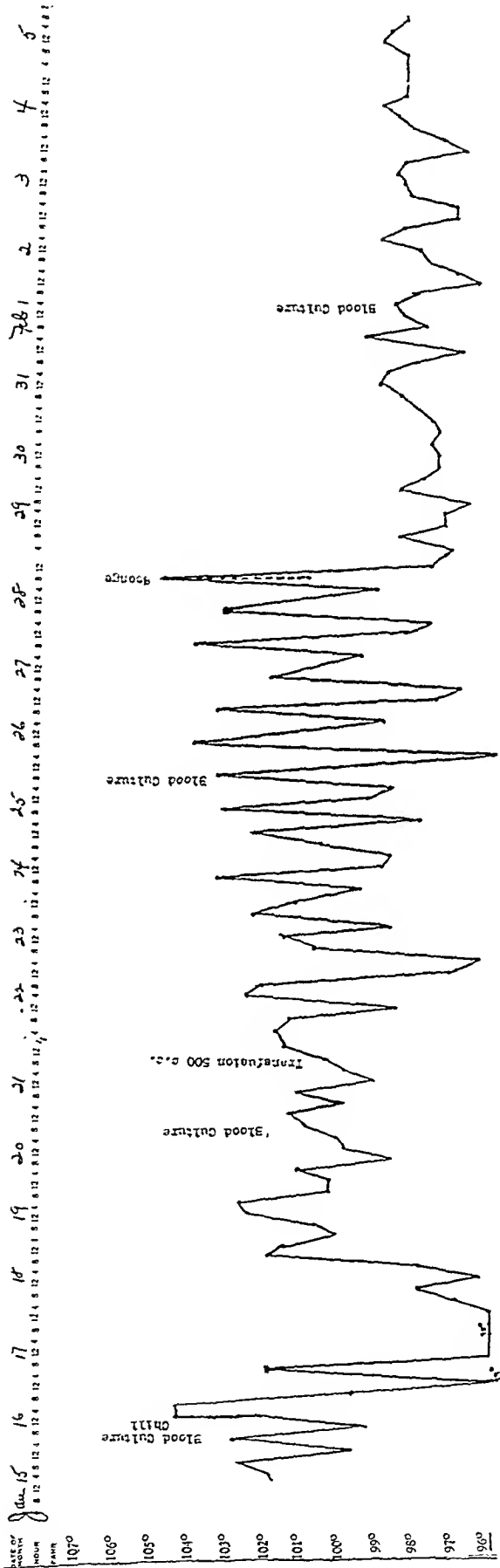


Fig. 1.

Clinical Course: The temperature the day of admission was 104.4° , following a short shaking chill. Blood culture taken after the chill revealed the presence of gonococci in all the fluid media. This finding was confirmed on three occasions. The gonococcus-complement fixation was four plus. Two days after admission, a soft diastolic murmur was heard over the sternum at the level of the third interspace. Three days later a white centered petechia was seen in the right lower conjunctiva. At the same time, a small red lesion, which was tender, appeared on the dorsum of the left foot—a metastatic focus. This lesion disappeared in two days. The anemia progressed, the hemoglobin dropped to 53 per cent. For the first week there was no recurrence of the chills. One week after admission a 500 c.c. transfusion was given, as a result of which the hemoglobin rose to 62 per cent. Eight days after admission, fluoroscopy of the chest was performed which revealed that the left ventricle was enlarged downward and to the left, and that there was some prominence in the region of the left auricle in the posterior anterior position, but no evidence of enlargement was seen in the right oblique position, the aorta was dilated, its excursions wide. The appearance was that of an aortic insufficiency probably associated with a mitral lesion. The blood pressure dropped from 108/70 to 90/30 mm. The endocardial murmur was observed to become more pronounced during the patient's stay. Profuse sweats occurred. The temperature ran a septic course (see chart, Fig. 1) for two weeks. On the fourteenth day after admission, January 28, 1932, the temperature rose to 104.8° at eight o'clock in the evening, to fall to 97.8° at midnight. It thereafter never rose to a point above 99.6° . Six weeks after admission, or four weeks after the defervescence of the fever, the spleen was found to have receded to a point one finger breadth below the left subcostal margin. The blood pressure on discharge was 120/58 mm. One week after the remission of the fever, the urine showed no albumin, no formed elements and was guaiac negative. Electrocardiogram revealed no definite abnormality. Blood culture taken on the fifth day after the remission of the fever was sterile.

Follow-Up Reports: March 28, 1932, blood pressure 110/30 mm. Patient felt entirely well. No dyspnea or swelling of the ankles. No Corrigan pulse present. No urinary complaints. Spleen palpable one and a half fingers below subcostal margin. May 23, 1932, patient felt entirely well, had had no dyspnea. No swelling of the ankles. No congestive signs in the lungs. A soft diastolic murmur was heard at the second left interspace transmitted along the left border of the sternum. Spleen felt one and a half fingers below subcostal margin. Heart slightly enlarged to left on percussion. Blood pressure 110/48 mm. June 27, 1932, patient felt well, had no complaints referable to cardiac or any other system. Examination of the heart revealed very short systolic murmur to second right interspace and an impure second sound to left of sternum in third interspace. July 25, 1932, patient felt perfectly well. There was no dyspnea or pulmonary congestion. Soft diastolic murmur was heard along the left sternal border. First heart sound loud. P_2 louder than A_2 . Blood pressure 140/60 mm. Spleen felt one finger below costal margin. July 26, 1932, Hemoglobin 90 per cent. October 24, 1932, patient perfectly well. Blood pressure 124/68 mm. Apical systolic murmur with accentuation of P_2 and very low-pitched diastolic murmur heard next to the sternum.

COMMENT

We were here dealing with a case of gonococcal endocarditis which developed in the course of a gonococcal bacteremia, following an induced abortion by tamponage and subsequently by curettage. This sepsis had run a chronic course of three and one-half months' duration preceding admission to the hospital. No valvular lesion was present

on admission nor was there anything in the past history of the patient, by direct questioning or by symptomatology to suggest antecedent valvular disease. During her course in the hospital which was markedly septic, an aortic and mitral insufficiency developed, confirmed by fluoroscopic examination and by an increase of pulse pressure under observation. The septic course went into spontaneous remission four months after onset; the patient having developed peripheral embolic phenomena, a focal glomerulonephritis, then went on to recovery and was discharged with an aortic and mitral insufficiency.

SUMMARY

Gonococcal endocarditis does not necessarily carry with it a fatal prognosis. The literature on reported cases of recovery in gonococcal endocarditis is reviewed in detail. A case of postabortal gonococcal sepsis with gonococcal endocarditis, with peripheral embolic phenomena, focal glomerulonephritis and valvular insufficiency which developed under observation and which underwent spontaneous recovery, is reported.

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RUPTURE OF THE AORTA*

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IN AN extensive review of eighty-three cases of rupture of the aorta with dissecting aneurysm, reported prior to the year 1863, Peacock¹ states that Mannoni first described the condition in 1802; however, the lesion was not generally appreciated until Laennec's work in 1826. A more recent survey made by Resnik and Keefer² shows a total of 200 reported cases. Much space has been given to the discussion of this condition by a number of competent men who have repeatedly covered the clinical and gross pathological aspects.

A classification of ruptured aortas based entirely on etiology is not possible with our present knowledge of the subject. Whitman and Stein,³ Shennan and Pirie,⁴ Resnik and Keefer,² Klotz and Simpson,⁵ and others, have suggested classifications. Most cases tend to fall into definite group which may be listed as caused by: (a) trauma, (b) extrinsic erosion, (c) hypoplasia, (d) coarctation, (e) inflammation, and (f) degeneration.

The confinement of fluid in any given space depends upon two factors, viz., the strength of the container and the pressure exerted upon it by the confined fluid. Both factors may be altered simultaneously in the human aorta; therefore, more than one important change may be present in any given case of rupture. Furthermore we must conclude, whether it can be demonstrated or not, that there has been an alteration of at least one of these forces. Klotz and Simpson⁵ found in testing aortas of individuals between the ages of twenty and forty years that a pressure of 1000 mm. of mercury was not sufficient to rupture its walls. Oppenheim¹³ found that rupture occurred at about a pressure of 3000 mm. of mercury in normal human aortas. Moritz¹⁴ found that pressures of from 800 to 1200 mm. of mercury induced through a cannula inserted in the proximal end of the aorta of living rabbits resulted in rupture of the portal vein or its tributaries. The aorta could not be ruptured because of the rapid flow of blood through its peripheral circulation. Sudden changes of pressure will have a much greater effect than a continuous force; consequently these figures are higher than those in the sudden tearing force necessary to burst the vessel. Cases of rupture of the aorta associated with chronic high blood pressure are relatively frequent (Lifvendahl,¹⁵ Oppenheim,¹⁶ Busse,¹⁰ Löffler,¹⁷ Strickland,¹⁸ McLean and Fiddes,¹⁹ and many

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others). Unquestionably altered blood pressure plays a very important rôle in rupture of the aorta; it must be of the greatest importance in cases associated with coarctation. From the above experimental data it is difficult to conceive of any blood pressure ordinarily present being sufficient to burst a normal aorta.

Trauma.—Terrific blows to the thoracic cage have repeatedly resulted in the rupture of aortas which have been considered structurally normal (Rolleston,⁴ Kemp,⁷ Griffiths,⁸ Jaffe and Sternberg,⁹ and Busse¹⁰). Flying objects such as blocks of wood or stone, train and automobile accidents, falls from high buildings, bridges and aeroplanes, have all been found the cause of bursting of the aorta. This result is apparently due to the sudden transmission of the force of the blow to the confined noncompressible blood. It is interesting that in traumatic ruptures, as in rupture due to other causes, the site of predilection is in the ascending portion of the arch and at the duct of Botalli, thus favoring either Rindfleisch's¹¹ theory that these areas being comparatively fixed are predisposed to injury, or Abbott's¹² belief that the aorta may be congenitally weak in these regions. Rupture of the aorta from any cause results in the formation of dissecting aneurysm in a majority of cases. This phenomenon of dissection of the aortic wall, we feel, is the result of the right angle deflection of the rupturing force due to the greater elasticity of the adventitia in the traumatic cases, and to degenerative changes in the media in addition to the elasticity of the adventitia in the nontraumatic cases.

Extrinsic Erosion.—The compact walls of large blood vessels are relatively immune to the penetration of bacteria and malignant tumor processes extending from surrounding organs. Rupture due to erosion of the aortic wall by such lesions as mediastinal tuberculosis, carcinoma of the esophagus and similar lesions of the lungs and vertebrae is not uncommon and because of its general recognition will not be discussed further.

Hypoplasia.—The rupture of hypoplastic aortas, a condition generally associated with status thymolympathicus, has been described by Richey,²⁰ George,²¹ Marine,²² and others. These congenitally small thin aortas show a diminution in the breadth of all three layers of the wall but especially of the media, otherwise the structure is not markedly altered. This weak vessel may not withstand even the normal variations of aortic pressure.

Coarctation.—Of the 200 cases of coarctation of the aorta summarized by Maude Abbott,¹² 38 patients died of spontaneous rupture of the aorta. In Oppenheim's²³ case the wall was apparently healthy and rupture was thought to be due to the effect of a sudden increase in pressure acting on the seat of election, i.e., just above the cusps. In all the other cases of this series examined microscopically there existed pathological processes in the aortic wall. The effect of a continuous high blood pressure

in the aortic arch is apparently of the greatest importance; there results a dilatation of the vessel with a marked thinning of the walls proximal to the coarctation, even to parchment paper thinness. There may be marked changes in the media consisting of interruption and diminution of the elastica with an increase of fibrous connective tissue; hyaline and frequently fatty degenerative changes are found. A great majority of these cases showed a dissecting aneurysm which ruptured secondarily into the pericardial sac or into an adjacent viscus.

Inflammation.—Intrinsic inflammatory processes, syphilitic and non-syphilitic, are not uncommonly the basis for rupture of the aorta. The gradual destruction of both elastica and muscle elements of the media, with subsequent fibrous connective tissue scarring and intimal sclerosis, and later dilatation of this weakened structure to aneurysmal proportions and rupture are frequent in syphilitic aortitis. Because of the apparent welding of the neighboring laminae by the connective tissue reaction in syphilitic mesaortitis, Klotz and Simpson⁵ feel that this disease plays no part in the production of true dissecting aneurysm. Tyson,²⁴ Tidmarsh,²⁵ Lifvendahl,¹⁵ and Gsell²⁶ report cases of dissecting aneurysm and rupture of aortas showing typical luetic mesaortitis without the usual marked dilatation of the aortic lumen.

Infections of the aorta, other than syphilitic, resulting in rupture are comparatively rare. The localization of infectious emboli in the aortic wall entering by way of the vasa vasorum, with abscess formation and at times mycotic aneurysmal dilatation and rupture has been described. Infectious endarteritis varying in its bacteriological findings occasionally develops in a *locus minoris resistentiae* afforded in the vicinity of a coarctation. A favorable nidus is provided here where the aorta is generally dilated, deformed and atheromatous. Poynton and Sheldon²⁷ have described such a case and collected four from the literature. Reifenstein,²⁸ Smith and Hausmann,²⁹ Libman,³⁰ and Narr and Johnson,³¹ have described similar cases with rupture.

It is rather surprising that the extensive muscular degeneration resulting from rheumatic aortitis as described by Pappenheimer and von Glahn,³² Sacks³³ and others does not result in rupture of this large vessel, but it undoubtedly does in smaller vessels. The rheumatic inflammatory process does not destroy the elastica, wherein lies the strength of the aorta. It will be noted that rheumatic fever cannot be excluded as the cause of rupture of the aorta in a case of Lifvendahl.¹⁵ The importance of infectious lesions in the destruction of the aortic media is vouched for by Wiesel³⁴ who noticed the presence of peculiar focal necrosis in the vessel wall of young individuals dying of acute infections. Klotz³⁵ believes that multiple bacterial emboli are the most important factor in the medial degeneration of arteriosclerosis. Many other authorities, including Gsell,²⁶ Erdheim,³⁶ Seheld,³⁷ Stoerek and Epstein,³⁸ Klotz,³⁹ Duff,⁴⁰ and Bailey,⁴¹ have suggested the

possible importance of bacterial toxins in the degenerative processes which may eventually terminate in rupture of the aorta.

Degeneration.—Intrinsic degenerative changes in the aortic wall leading to its rupture may be divided into the (a) arteriosclerotic and (b) medial degenerative types.

(a) Of the eighty cases of ruptured aorta collected by Peacock,¹ forty-two had arteriosclerosis. MacCallum's¹² five cases all showed advanced arteriosclerosis. Similar cases of Gager,⁴³ Gallagher,⁴⁴ Thorpe,⁴⁵ Sheldon and Dyke,⁴⁶ Tyson,²⁴ Maitland,⁴⁷ Strickland,¹⁵ Lifvendahl,¹⁵ Kaufman,⁴⁸ and many others stress the importance of arteriosclerosis as a cause of spontaneous rupture of the aorta. A great majority of the aortic tears occurring after the age of forty are due to arteriosclerosis. Adami¹⁹ cites Aschoff, Klotz and Foster in describing physiological changes of the aorta, an increase in elastic fibrils in number and size up to thirty-five years of age when their development becomes stationary for fifteen years. After fifty years there is noticed a slow progressive atrophy of the elastica as well as fatty degeneration of muscle fibers. Small calcareous granules are seen in some of the cells followed by necrosis and their complete absorption. The remaining elastic elements are thus allowed to stretch, losing their wavy appearance and elastic quality. Mackenzie has demonstrated a gradual disappearance of capillaries with advancing age resulting in degenerative changes in the places with poorest blood supply. The aorta of a child is quite elastic, and its lamellae are firmly bound together so that they cannot be separated. On the other hand, the aortas of old age lack elasticity and possess an unusual dryness and friability so that their walls can occasionally be separated without difficulty.

Among the many etiological requirements of arteriosclerosis perhaps those of greatest importance are: (a) increased functional demand, (b) injury to the wall by infectious and toxic influences, (c) nutritional and metabolic disturbances, and (d) familial and hereditary predispositions. These subjects we cannot enter upon here.

The arteriosclerotic process may have its onset in fibrous connective tissue proliferation of the intima, with subsequent degenerative changes of a fatty and hyaline nature and with calcium and cholesterol crystal deposits, necrosis, ulceration and rarely true bone formation. The media may participate with fatty degeneration, atrophy and necrosis of both muscular and elastic elements, especially in areas underlying intimal plaques. Later chalky connective tissue masses replace the lost medial elements. Perivascular fibrous connective tissue proliferation with round cell infiltration may be difficult to distinguish from a syphilitic lesion. At post-mortem examination the eggshell-like intimal layer may crack and split away on the slightest provocation. It is surprising that dissecting aneurysm with rupture or with re-

entrance of the lumen and healing (Hall⁵⁰ and Cleland⁵¹) is not more common, considering the number of severely atheromatous aortas seen at the autopsy table.

It should be pointed out that a primary intimal tear is not always a complement necessary for rupture. Tyson,²⁴ citing a few cases of his own and of others, stressed the point that dissecting aneurysms begin by hemorrhage from the vasa vasorum as a result of medial degeneration and that a tear in the intima of the aorta is not a necessary factor in the formation of such aneurysms. Furthermore he feels that when intimal tears do occur, they are probably secondary to the development of the aneurysm.

(b) Of the many causes for rupture of the aorta, that due to primary degeneration of the media is of the greatest pathological interest. There may be several types of medial degeneration, including (1) that of Gsell and (2) that of Babes and Mironseim. Of these that of Gsell stands out as an accepted histological entity. Gsell²⁶ first described the condition in 1918 and later Erdheim,³⁶ reporting two cases, gave it the name "*medio necrosis aortae idiopathica cystica*." Since then about twenty cases in all have been reported by various authors, including Klotz and Simpson,⁵ Tyson,²⁴ Moritz,¹¹ and Levinson.⁵⁷ This degenerative change of the media is not necessarily associated with any atherosclerotic changes in the intima and occurs in young adults as well as in older people. It is characterized by necrosis of the media and at times of the intima. Usually it is found only in the aortic arch but is especially marked in the ascending portion where the rupture and dissection of the media invariably begin. Occasionally the whole aorta is involved. Practically all deaths in this condition were due to cardiac tamponade due to secondary rupture into the pericardial sac. Histologically there is a bland patchy or bandlike necrosis, most marked in the middle portion of the media, affecting first the smooth muscle cells, with karyorrhexis and then complete necrosis, leaving a pale acidophilic homogeneous material. Later the more resistant connective tissue cells and elastica stain poorly, fragment and gradually fade into the same homogeneous light pink staining debris. Moritz¹⁴ following Schultz describes this tissue as chromotrophic substance and believes that it is deposited about the elastic fibrils and predisposes to their degeneration. The aorta may rupture at this stage or the degeneration may proceed to cyst formation. Erdheim³⁶ describes a healing process in which the cystic areas contain scattered stellate connective tissue cells (not scar tissue), or the healed areas may liquefy to form serous cysts. The process from the onset is free from inflammatory cell infiltration, there may or may not be fat droplets in the smooth muscle cells and about the elastica. Moritz¹⁴ found finely granular deposits of calcium in the chromotrophic substance.

The pathogenesis of medial necrosis is debatable. Tyson²⁴ describes occlusion of the vasa vasorum, due to intimal proliferation, with medial degeneration the result of nutritional disturbances. Klotz,²⁵ Moritz,¹⁴ and others agree that the necrosis is not to be explained in this manner. Moritz¹⁴ found chromatrophic substance in six of seventy adult aortas and suggests an involutional or senescent change. Theories of exogenous poisons (adrenalin and nicotine), poisonous products of metabolism and vitamin deficiency have been advanced. Duff¹⁰ has demonstrated medial changes in animal experiments following the injection of diphtheria toxin; these are said to be very similar to the patchy medial destruction in man. Unusually frequent or severe infectious diseases have not been elicited in the histories of these frequently healthy appearing individuals with medial necrosis. The solution awaits further investigation.

Babes and Mironescu⁵³ describe as a disease entity, "Mesarteritis dessecans," a very unusual type of degeneration in the aorta. Their case is from a fifty-one-year-old woman who died suddenly of a ruptured aorta. In the media of this vessel were small foci of thickened elastic fibers enclosing spindle-shaped clefts. There were systems of confluent clefts, where the elastic fibers were torn, and about these were large mononuclear cells and small hemorrhages; here and there were areas of fatty degeneration which at first were localized exclusively in elastic fibers. The heavier lamellae were enclosed in fat, while the smaller fibers contained fat, and this increased at the expense of the elastic tissue. There were some calcareous changes, connective tissue proliferation, round cell infiltration about the vasa vasorum and sclerotic changes in the intima.

In reading the descriptions of the microscopic examinations of reported cases of rupture of the aorta one finds instances which do not fit into the classification noted above. Apparently there are other less distinct types of degeneration of the aorta. There are also a number of spontaneous ruptures reported where the authors vouch that there were no gross or microscopic changes (Kaufman,⁴⁶ Riehey,²⁰ Loebler,¹⁷ Pasckis,⁵⁴ Snss,⁵⁵ Arenberg,⁵⁶ and others).

CASE REPORT

The patient was a married physician, twenty-nine years old. He was admitted to Research Hospital, service of Dr. Robert C. Davis, complaining chiefly of severe precordial pain of four days' duration. He had had smallpox at six years, tonsillitis five years ago, occasional attacks of grip, and pertussis in the summer of 1932. He had been a rather heavy drinker of alcoholic beverages and had been known to indulge in breathing ether and chloroform vapors. His systolic blood pressure had varied from 130 to 170 mm. during the last few years. His wife and two children were in good health; the family history was essentially negative.

The patient had apparently been in good health until seven days before his death when, while shaving, he had a sudden extremely sharp pain over the precordium followed by vertigo, dyspnea, pallor and marked weakness. In spite of large doses

of opiates, the pain remained severe through the night. The next day he rode 200 miles in a car and did some dancing. During the next two days he was confined to his bed, had four or five mild chills with fever, and developed petechiae in the left axilla. On admission to the hospital he was orthopneic and extremely restless. He had a nonproductive cough, vertigo, general aching and marked perspiration. His respiratory rate gradually increased during his three days in the hospital from 20 to 45 per minute. The pulse remained about 125 and his temperature was irregular in its variation from 97° to 101° F. The physical examination was essentially negative except for a moderately enlarged heart, with a precordial thrill and a harsh blow filling systole and most of diastole, heard over the entire chest but best at apex. There were a few blotchy fading petechiae in the left axilla. Blood pressure was 134/70 mm. Radiological examination indicated increased fluid in the pericardium and some cardiac hypertrophy. Routine blood and urine analyses were essentially negative. The Wassermann test was negative. Repeated blood cultures showed no growth. Electrocardiographically there were marked right ven-

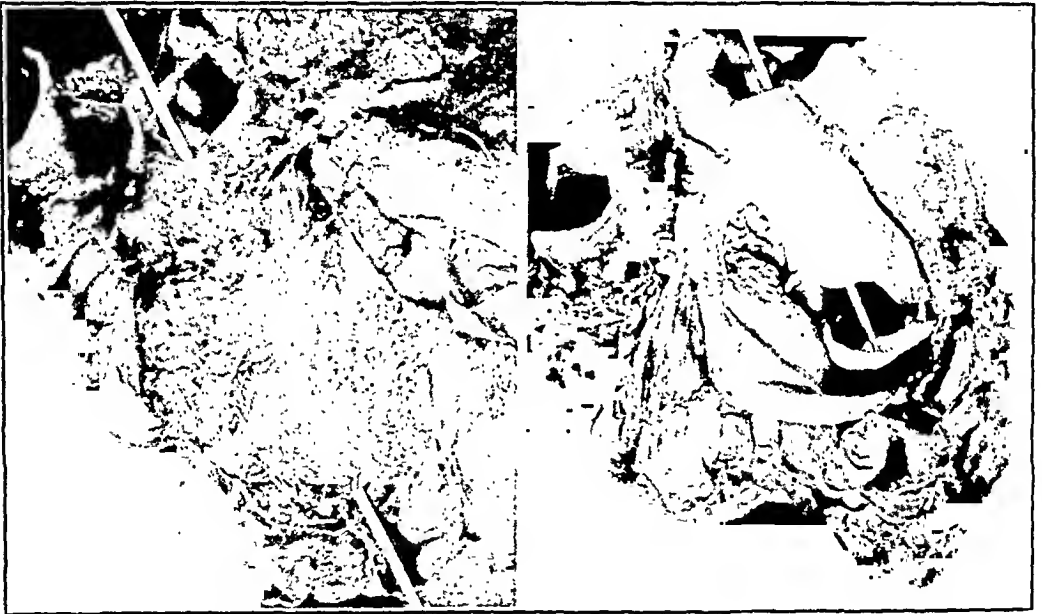


Fig. 1.

Fig. 2.

Fig. 1.—Small tear of adventitia of aorta within a centimeter of its base. Probe passes through this tear into dissecting aneurysm.

Fig. 2.—The outer wall of the dissecting aneurysm opened and edges spread to show the separation of adventitia from media in lower portions and separation of several layers of media in upper portion, as well as horseshoe rent of intima and media a few millimeters above the aortic valves.

tricular predominance, notched P_2 , negative P_3 , and an increase in the ventricular conduction time. The patient died suddenly on his seventh day of illness.

Autopsy.—The heart weighed 500 mg. The pericardial cavity contained approximately 500 c.c. of dark red, friable blood clot. The pericardial surfaces were covered by flakes of fresh fibrin which were easily torn away from the surface. There were no fibrous adhesions and no gross evidence of an acute inflammatory process. A small tear, measuring about 0.6 cm. in diameter, was found in the adventitia of the aorta within 1 cm. of its base. Further exploration revealed a communication through this hole directly into a dissecting aneurysmal cavity located between the adventitia and media in places and between the outer layers of the media in others, extending entirely around the aorta excepting for 2 cm. on the concave aspect where the layers had not been separated, and extending up the main branches of the

aortic arch for a short distance, involving the entire aortic arch and about 5 cm. of the thoracic aorta at which point it re-entered the lumen of the aorta. There was a horseshoe-shaped rent through the media and intima on its anterior and right lateral aspect, the two points beginning within a few millimeters of the level of attachment of the aortic valves, extending 3 cm. upward on one side and 2 cm. on the other, the two lines communicating by a curved line about 3 cm. long. The exposed inner surface of the adventitia was a dark red color and showed deposits of fibrin. The intima showed a few small scattered yellowish plaques located in the first 2 cm. of the ascending aorta, the largest of which measured 3 mm. in diameter. The aorta measured 9 cm. in circumference at its valves. The aortic end of the ductus arteriosus was patent, into which a 1 mm. probe could be inserted to the point of occlusion in the wall of the pulmonary artery. There was a definite smooth constricting band located at the level of the left subclavian artery (coarctation); at this point and beyond it the aorta measured 4.5 cm. in circumference. The aortic valves showed rather extensive fenestration, and there was a slight increase in their fibrous tissue. The mitral valve showed a definite thickening of its edges due to



Fig. 3.—Weigert's elastic stains showing bulbous swellings of elastica and degeneration of muscle fibers.

connective tissue proliferation and firm translucent nodules along the entire edge, some measuring 2 mm. in diameter. There was possibly slight shortening of the chordae tendineae of this valve. The left ventricle was moderately dilated as was the left auricle. The remaining two valves showed no lesions. The endocardial surfaces were not changed excepting for a reddish blotchy discoloration underlying the endocardium of the right auricle in the immediate vicinity of the ruptured aorta. The myocardium of the left ventricle was considerably hypertrophied and had a normal consistency; it showed no fibrosis. The coronary arteries showed a moderately advanced atherosclerotic process, with calcium deposits, for a distance of about 6 cm. from their onset, but no point of occlusion.

The lungs showed a moderate congestion of their lower lobes and were otherwise normal. The liver weighed 2150 grams and was moderately congested. The spleen weighed 240 grams, its pulp was soft, congested and granular. Lymph nodes in mesentery, mediastinum, and especially those at the base of the heart, were moderately enlarged, frequently measuring 1.5 cm. in diameter. The other viscera showed no gross changes.

Microscopic Examination.—Heart: Multiple sections taken from this organ showed the muscle fibers well stained and their cross striations distinct. The nuclei showed no changes. There was slight increase in the amount of interstitial connective tissue. The pericardium showed slight thickening, possibly due to edema, and also had a scattered lymphocytic and plasma cell infiltration. Occasionally small flakes of fibrin were seen on the pericardial surface. Sections through the coronary arteries showed an advanced sclerotic process characterized by marked intimal thickening throughout the circumference of the vessel, which appeared as degenerated or necrotic tissue arranged in a bizarre manner and taking a slight pink stain. This degenerative change involved the entire intimal layer of most of the circumference and the media, except for a few muscle fibers in its outermost layers.

Aorta: Sections taken from the immediate vicinity of the rupture showed an extensive retrograde process involving especially the central portion of the media,

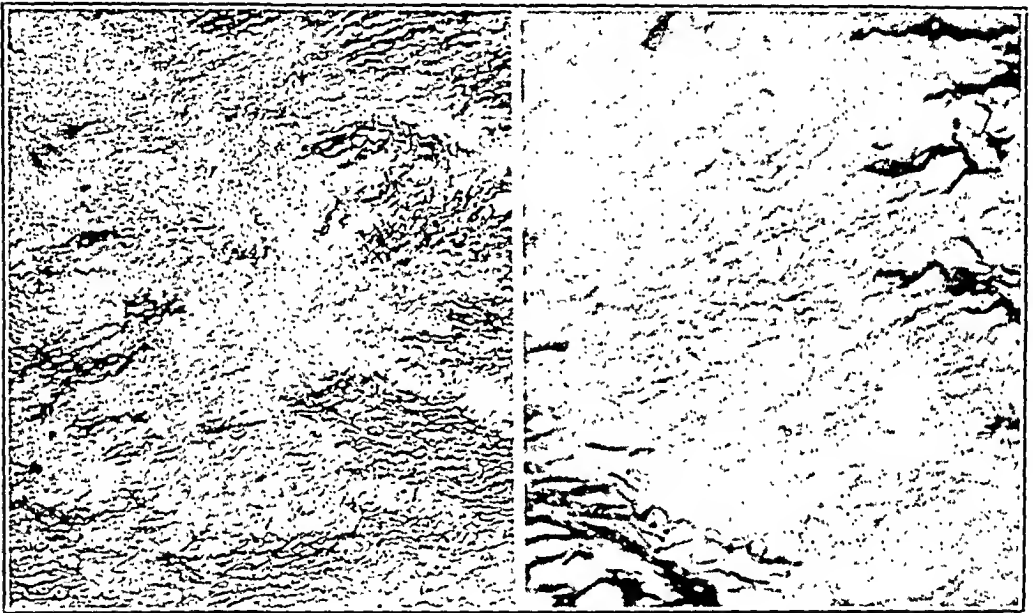


Fig. 4.

Fig. 5.

Fig. 4.—Weigert's elastic stain (low power). Medial necrosis with loss of elastic and muscle fibers and their replacement by homogeneous and fibrillar material.

Fig. 5.—High power magnification of Fig. 4.

where there was a bandlike necrosis. In places this extended to involve the entire media and intima, and in others it was patchy in its distribution. These very markedly involved areas were characterized by complete loss of cells, there remaining only a very light pink staining shadow of a few of the former cells and elastic fibrils. As stated, this necrosis of the tissues was evidenced primarily in the medial portion of the media; however, in the same section one could notice a similar process diffuse and patchy in its distribution, involving the entire media, and at times the intima, throughout the sections taken from the ascending portion of the aortic arch. There was a marked diminution in the number of cell nuclei and elastic fibrils throughout the media, including the areas not necrotic. Sections taken from the descending portion of the aortic arch showed a much less involved tissue; however, there was still a central band of apparently necrotic medial cells of rather narrow breadth. Sections from the thoracic aorta showed an entirely normal cellular and elastic structure. The vasa vasorum in both the adventitia and media showed only sparse cellular infiltration, amounting to an occasional lympho-

cyte or monocyte. This infiltration was more extensive in the immediate region of the dissecting aneurysm. In a few sections where the dissection was between the media and adventitia one found definite long cracks running in the longitudinal bandlike necrotic area of the media. Lining the aneurysmal walls was a rather thick layer of fibrin, and at times one would find fibrin in the cellular tissues in the immediate vicinity of the aneurysmal sac as well as small accumulations of red blood cells. Weigert's elastic stains showed almost complete loss of the staining properties of fibers in the regions of necrosis described above. The elastic fibers in other regions of the arch were badly fragmented and frequently showed bulllike swellings. Fat stains showed only rare small fatty deposits anywhere. Sections taken a short distance from the dissecting aneurysm showed no hemorrhages and no neutrophilic infiltration. There was no connective tissue proliferation in any of the three layers. Cyst formation, occlusion of vasa vasorum or attempts at healing could not be found.

Microscopic study of other organs revealed a chronic passive congestion of the lungs and spleen but no other significant changes.

CONCLUSION

We consider this a typical case of idiopathic medial necrosis with rupture of the aorta. As is usually the case, it occurred in a young, apparently healthy and active adult, having had no unusual or severe illness in his past. In this case there had been considerable dissipation, with an excessive use of alcohol, nicotine, ether and chloroform. An etiological significance of the healed rheumatic lesion of the mitral valve is considered unlikely, also a mild degree of concretion may have been a contributing factor by increasing the blood pressure proximal to the constriction. Except for the extensive degenerative changes in the coronary arteries other blood vessels were not affected. Evidence of an infectious process in any organ is lacking. In this case, as is almost invariably true in the reported cases, the intimal tear was in the ascending arch, and the patient died of cardiac tamponade when the dissecting aneurysm ruptured.

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DESCRIPTION OF A MON-AURAL DIAPHRAGM TYPE OF STETHOSCOPE WITH DISCUSSION OF ITS SPECIAL FIELD OF USEFULNESS*

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IT IS probable that marked variations in sound perception exist in individuals with apparently normal hearing. These, apart from changes in the auditory apparatus, may be due to certain atmospheric conditions, fatigue, and congestion of the upper respiratory tract. Because extrinsic influences are variable it is difficult to appraise the efficiency of hearing, especially in the perception of fine gradations. This is in contrast with purely mechanical devices in which transmission and reception of sound are controlled and studied with nice precision.

Since few individuals hear exactly the same under all conditions, questions arise as to the efficiency of instruments for magnifying and conveying vibrations which are heard as sounds. In stethoscopes the comparative value of the so-called bin-aural bell type and the diaphragm type has been widely discussed. The accuracy of the "bell" for the study of vesicular and loud bronchial sounds, râles and low pitched, rumbling, crescendo heart murmurs is recognized. Differences of opinion exist chiefly in the elicitation of high pitched, faint, blowing heart sounds of aortic insufficiency and faint, high pitched "bronchial" respiratory sounds. These, according to some observers, are heard satisfactorily with the diaphragm model. In order to obtain the advantages of both types the "bell" and "diaphragm" have been incorporated in the same instrument. This is convenient and satisfactory for general use but criticisms have been noted. It has been found especially that reception from the diaphragm sector is less distinct than from the single diaphragm model, and the bell sector gives marked exaggeration of the finer tones. This is attributed to the lack of insulation between the two sectors and to one part's acting as a resonator for the other part.

In reviewing the writings of early clinicians, especially Laennec, one is impressed with important observations made with the ear alone or the simple stethoscope. It may appear in comparison that the refined instruments of the present day are not giving all the information that can be obtained. This was emphasized by L. A. Conner¹ in

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an interesting paper on the limitations of the stethoscope. He pointed out that sounds which are faintly heard or missed entirely may be heard clearly and sharply with the ear alone. A similar view was expressed by L. F. Fliek² who has observed in studying diseases of the lungs for over fifty years that soft blowing bronchial sounds existing in the presence of vesicular sounds are lost through the bin-aural stethoscope but with practice may be heard clearly with the mon-aural type.

It appears from these considerations that one stethoscope may not be suitable for all examinations. The ear alone, as pointed out by Conner, should be used far more frequently than is done by the younger physicians. Due to certain objections, which are largely questions of delicacy, hygiene or inconvenience, the use of some mechanical device is often required.

In the development of the stethoscope to be described, an attempt has been made to utilize, so far as possible, the mechanisms of air and bone conduction which are features of the ear alone and the mon-

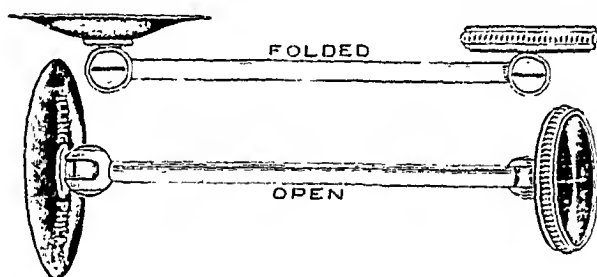


Fig. 1.—The upper illustration shows the instrument with the ear and chest pieces folded (for carrying) against the stem. In the lower illustration the ear and chest piece assemblies are open for use. The ball-and-socket joint construction is shown.

aural stethoscope. The effects of metal, rubber and wood conducting media were especially studied. Soft rubber was eliminated because of its damping effect. Metal was selected in preference to wood because it has peculiar values in transmitting sounds with a ringing quality. It is generally as satisfactory as wood for the transmission of other sounds and is especially suitable for good workmanship.

DESCRIPTION OF A METALLIC MON-AURAL DIAPHRAGM STETHOSCOPE

A standard diaphragm type of chest piece (Bowles) was modified as follows: (Fig. 1.) The weight of the chest piece was reduced one-sixth, the clefts were obliterated, the dome increased to 3.5 mm. in depth. The chest piece diameters of 2.5 and 4.5 cm. (two sizes) were retained. The opening between the chest piece and the stem was bored to a diameter of 2 mm. A circular base 1.5 mm. in width was ground for contact with the diaphragm. A hard rubber ring was screwed to the circular base and holds the diaphragm flush with the base. The rubber ring provides a warm surface for contact with the chest wall and when removed the instrument is converted into a "bell" stethoscope. The stem (12 cm. in length) was made from heavy brass tubing, the lumen was bored to a diameter of 1.5 mm.

One end of the tubing was connected with the chest piece by means of a ball-and-socket joint, the other end, in a similar manner, to the ear piece assembly. The ear piece consists of a hard rubber disc 6.5 cm. in diameter molded to fit over the lobe of the ear. The ball-and-socket joints have counter sunk construction which provides an opening through the joints when the chest and ear pieces are turned to any angle up to 30° . Because of this mechanism the instrument can be adjusted

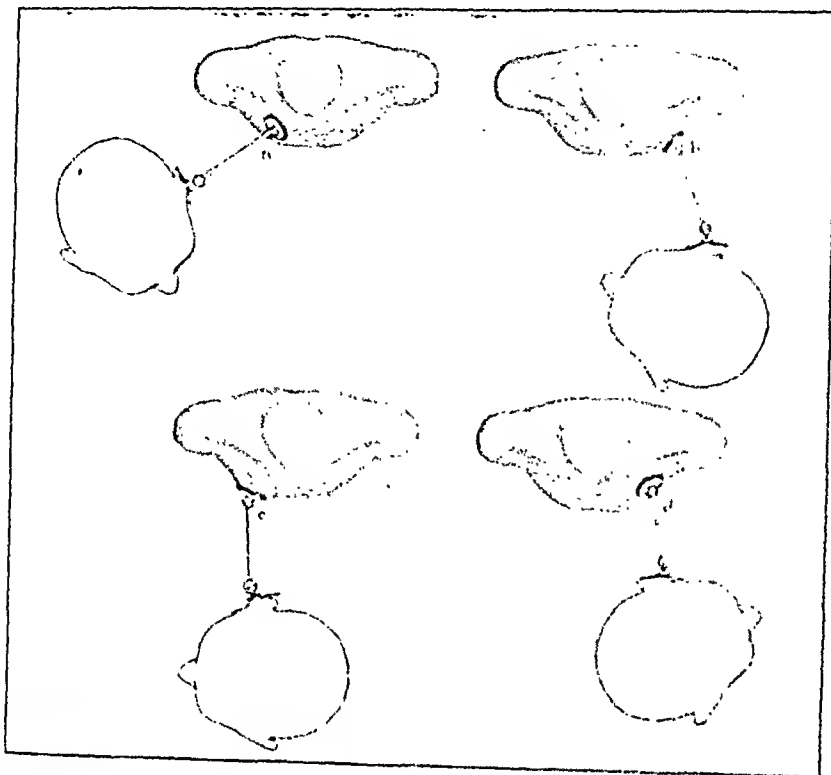


Fig. 2.



Fig. 3.

Figs. 2 and 3.—Showing the various positions of the examiner's head when studying remote parts of the chest.

easily for the study of remote parts of the chest. Tension springs are placed in the joints to prevent accidental turning of the ear and chest piece assemblies during the examination. For carrying in the pocket the ear and chest pieces may be "folded" against the stem.

As in the evaluation of all stethoscopes, the question of individual preferences as well as the influence of physical laws must be considered. As compared with the bin-aural diaphragm type in the study of heart murmurs there is less distortion of sound and usually finer definition. It is useful especially in the eliciting of aortic murmurs, and the results are comparable with those obtained with the ear alone. Certain accentuating sounds existing in the presence of humming or blowing noises may be heard with striking clearness. Amplification is usually greater than in the mon-aural bell type. In studying the lungs a most helpful feature is the transmission of soft blowing bronchial sounds and râles with a ringing quality. Clinical trials do not suggest that the instrument should replace other stethoscopes or the ear alone but rather that it may be employed as a supplementary instrument.

Remarks by Dr. Thomas McCrae.—It has been interesting to compare this mon-aural stethoscope made of metal with the usual one made of wood. The transmission of sounds is somewhat different and on the whole the mon-aural metal stethoscope impresses me as being more useful than the wooden one. It is unfortunate for our education in auscultation that the mon-aural stethoscope is so rarely used. After all the only advantage of the bin-aural stethoscope consists in its being more convenient. The mon-aural instrument transmits certain sounds much better. No one should regard his education in the practice of auscultation as complete until he has learned to use a mon-aural stethoscope. For the auscultation of the heart it has many advantages; one feels the impulse at the same time as one hears the sounds. One has to learn to disregard sounds which enter by the unengaged ear, just as the impressions received by the eye which is not used with a microscope with a single eyepiece are not perceived. The other eye is kept open but the images do not register. It has often interested me to see the surprise shown by a man who uses a mon-aural stethoscope for the first time, as many regard it as an antique instrument of historical interest only and markedly inferior to the bin-aural form; a trial usually shows the contrary. If you are one of the unfortunates who has to close the other ear to hear what is transmitted by the mon-aural stethoscope, then, of course, it is not so useful.

While Dr. Gordon has emphasized the employment of this instrument in the auscultation of the heart, my feeling is that for the study of certain pulmonary sounds it has distinct advantages. One cannot describe the differences in sounds; only an individual trial can demon-

strate them. The use of the mon-aural instrument is well worth while by every one who wishes to improve himself in auscultation. It would be a good thing if every interne had to use a mon-aural stethoscope for a time. It may be added that many of us forget that direct auscultation is often valuable. It should be used more than it is.

COMMENT

The failure of the bin-aural stethoscope to transmit effectively the soft blowing high pitched heart murmurs and certain pulmonary sounds has been noted. It has been observed in contrast that these may be heard clearly and sharply with the ear alone or with a mon-aural stethoscope. A mon-aural diaphragm type of stethoscope which utilizes the mechanisms of air and bone conduction and is easily adjusted for the special examination of remote parts of the chest is described. With practice the instrument is especially effective in transmitting soft blowing and ringing sounds and certain other phenomena not clearly heard with the bin-aural "bell" or "diaphragm" stethoscope.

The instrument is manufactured by the Geo. P. Pilling and Son Company, Philadelphia.

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REPORT OF A CASE OF PAROXYSMAL VENTRICULAR FIBRILLATION IN RELATION TO QUINIDINE THERAPY*

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THE beneficial effect of quinidine sulphate in the treatment of tachycardias of ventricular origin is well recognized. There are numerous reports of cases in which the ventricular tachycardia has been stopped or the frequency of the attacks greatly diminished by its use. This subject has recently been well reviewed by S. A. Levine and Fulton.¹

The relation of quinidine sulphate administration and ventricular fibrillation is not so clear, primarily because of the rarity of the condition and the difficulty in making clinical observations as to the efficacy of such treatment. Kerr and Bender² report a case in which attacks of ventricular fibrillation occurred when quinidine sulphate was administered, and Davis and Sprague³ report death from ventricular fibrillation in the course of quinidine therapy. Doek,⁴ however, reports a case in which a maintenance dose of quinidine prevented attacks of paroxysmal ventricular fibrillation. Furthermore, H. D. Levine⁵ recently demonstrated in the experimental animal that quinidine has an inhibitory effect on ventricular fibrillation and makes it more difficult for the irregularity to develop than in the control unquinidized animals.

This case is being reported because of the comparative rarity of paroxysmal ventricular fibrillation, and as an illustration of the effect of quinidine sulphate in the condition.

CASE REPORT

J. D. (Med. 41316), a sixty-year-old, white, unmarried janitor was first admitted to the medical service of the Peter Bent Brigham Hospital on June 23, 1932. He complained of "fainting spells."

The family history was not remarkable except that one brother and one sister died of cardiovascular disease. The past history was negative. There was no history of rheumatic fever or syphilis.

The present illness began two years before when he first noted a feeling of fullness in the epigastrium which seemed to rise and cause a sensation of pressure in the throat. He thought he had "indigestion." Following one of these attacks he lost consciousness for a few minutes. He then consulted his physician who discovered hypertension and put him on a diet. No digitalis was given. His attacks of discomfort decreased in number, but during these two years he had two more "fainting spells." Four months before entry he noticed that the attacks of fullness in the epigastrium were accompanied by some numbness and tingling in the left arm.

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On the day before admission he experienced such an attack and that night, while walking from one room to another, he suddenly became very dizzy and faint and fell to the floor. According to family reports he was unconscious for about fifteen minutes. He then remained in bed, but on the morning of entry had another attack of syncope shortly after awakening. There were two more "fainting spells" before admission that afternoon. He denied having experienced any precordial pain or palpitation and between attacks had noted no dyspnea, orthopnea or ankle edema. He had continued his work as a janitor in a lithographing plant until he was laid off two months before admission.

Physical examination revealed that the patient was moderately obese and in no apparent discomfort. The optic fundi showed moderate evidence of retinal sclerosis. The heart was moderately enlarged, with a diffuse apex impulse. The left border of dullness was 11.5 cm. from the midsternal line; right border of dullness was

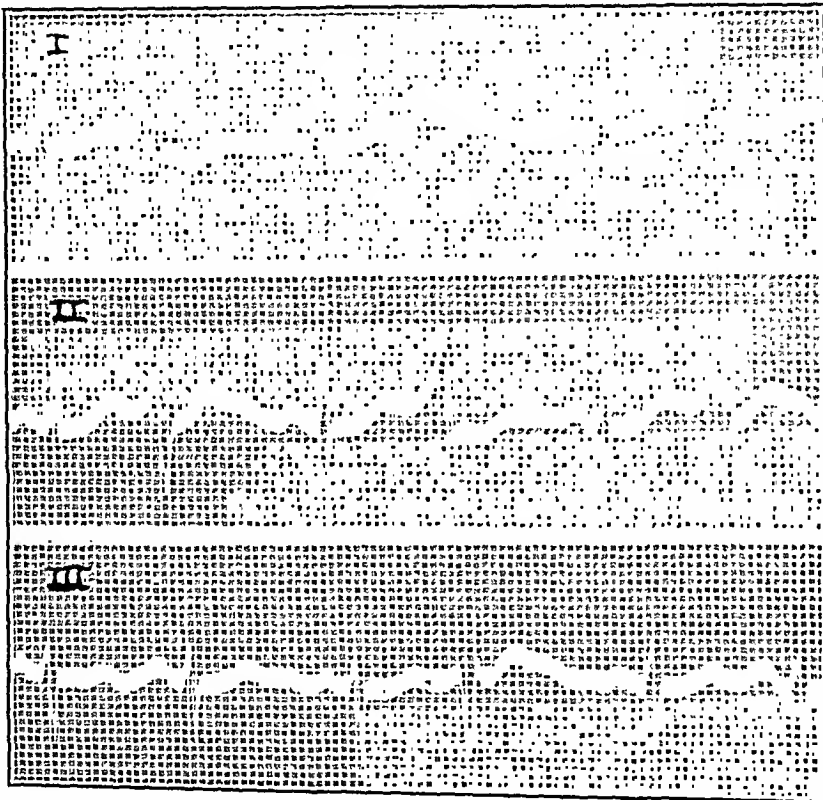


Fig. 1.—(Leads I, II, and III) Taken shortly after admission on June 23, 1932. Showing the occurrence of frequent ventricular extrasystoles, at times simulating coupling.

just outside the right sternal margin. At the apex the heart sounds were of good quality, but at the base they were somewhat distant. There was a soft systolic murmur at the apex. The rhythm was regular except for occasional extrasystoles and the rate was 80 per minute. The lungs were clear and the liver was not enlarged. No edema of the extremities or sacrum was present. Blood pressure was 150 mm. systolic and 80 mm. diastolic.

Laboratory Findings.—Blood—Hgb. 74 per cent (Sahli), R.B.C. 4,410,000 per c. mm., W.B.C. 18,600 per c. mm. of which 95 per cent were polymorphonuclear cells. Urine—very slight trace of albumin. The sediment showed numerous hyalin and granular casts. The Wassermann and Hinton reactions of the blood serum were negative. Blood urea nitrogen 17.9 mg. per cent. Phenolsulphonephthalein excretion in two hours and ten minutes (intramuscular injection) was 55 per cent in 80 c.c. of urine.

A seven-foot roentgen-ray examination of the heart thirteen days after admission showed enlargement both to the right and to the left with a rather blunt ventricle suggesting hypertrophy. The aorta was tortuous but not dilated. Fluoroscopic examination showed a regular vigorous beat with a fairly marked expansion of the aorta. The cardiac measurements were: Midline to right border 6.1 cm., midline to left border 9.3 cm., great vessels 5.5 cm., internal diameter of the chest 29.8 cm.

Course During the First Admission.—On the afternoon and evening of admission the patient had three attacks of syncope and numerous attacks of transient vertigo. Clinical observation disclosed that the normal rhythm was never free of occasional extrasystoles, and preceding an attack of vertigo these would increase in number

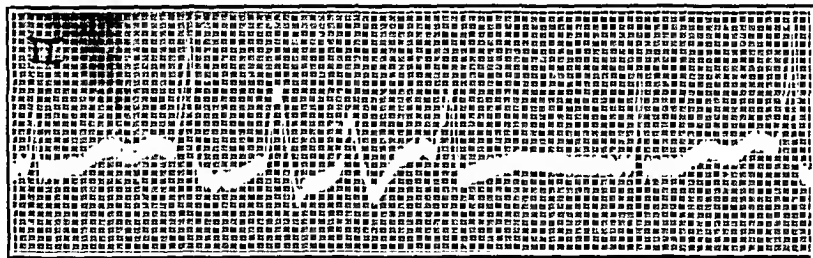


Fig. 2.—(Lead II only) Showing increasing numbers of extrasystoles which generally preceded attacks of ventricular tachycardia.

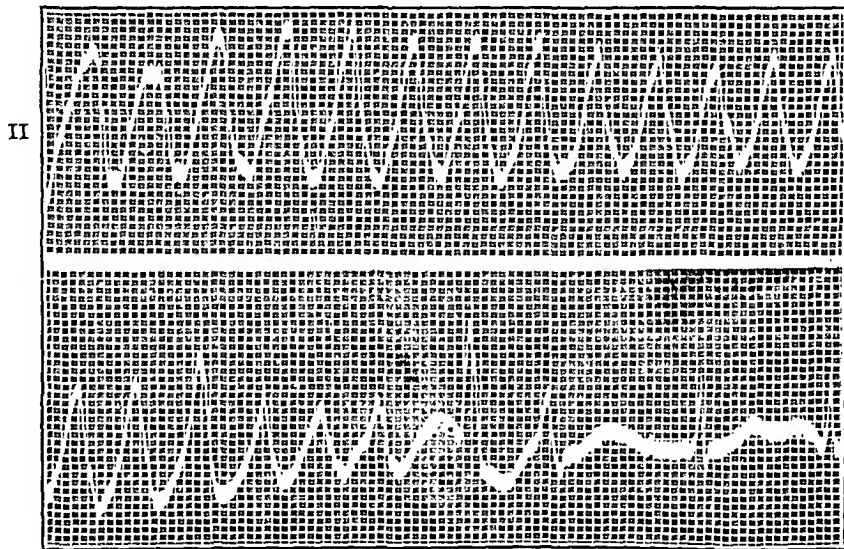


Fig. 3.—(Lead II only.) A continuous strip and shows approximately the last half of an attack of ventricular tachycardia with recovery and return to normal rhythm. The total duration was ten seconds and the rate reached 214 per minute. It was during these attacks that the patient felt agitated and dizzy and complained of epigastric fullness.

so that the rhythm became very irregular. This would finally lead to a short tachycardia lasting from seven to eleven seconds during which the rate was 180 to 200. At this time the patient became very agitated, dizzy and moderately cyanotic. He complained at such times of a feeling of fullness in the epigastrium rising to his throat and causing a sensation of pressure there. These were similar to attacks he had had before entering the hospital. The tachycardia stopped abruptly and was followed by a diminishing number of extrasystoles; the heart gradually returning to its normal rate of about 80. Several of these attacks of tachycardia with the transition to and from normal rhythm were recorded by the electrocardiograph.

The syncopal attacks started in the same way except that after a short tachycardia the heart sounds and pulse disappeared. At this point his breathing would become stertorous and his color livid. The eyes were rolled back and he would thrash about on the bed. The duration of the attacks varied from fifty seconds to three minutes, and during the longer periods respirations ceased after approxi-

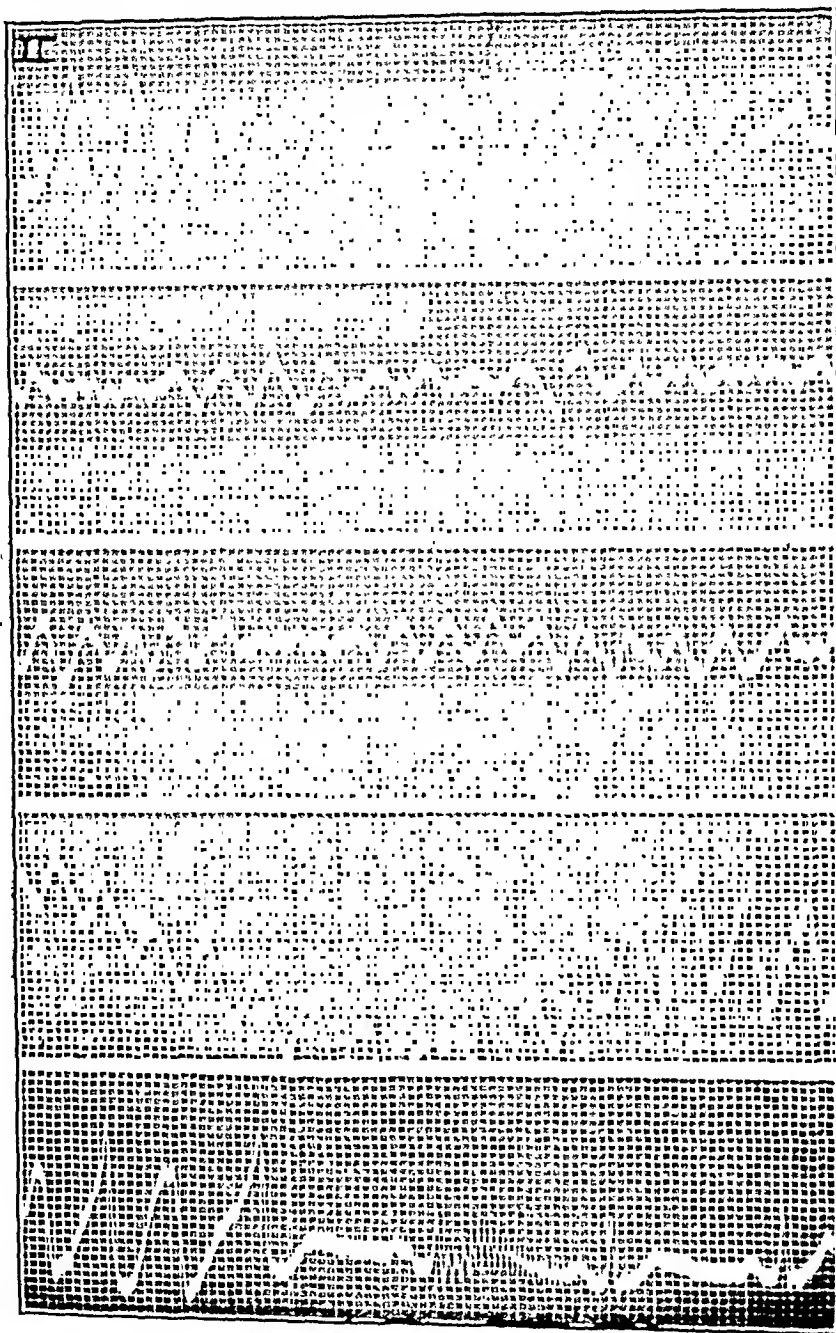


Fig. 4.—(Lead II only) shows sections from an attack of ventricular fibrillation. The first strip shows the end of the tachycardia which preceded the fibrillation and the beginning of the fibrillation. The second and third strips were picked at random and are typical of the fibrillation which persisted for approximately ninety seconds. The fourth and fifth strips are continuous and show the end of the attack with a change to a short run of tachycardia and then the sudden reversion to a normal rhythm.

mately one and one-half minutes. The attacks would end with the return of the heart sounds which were pounding in character and very rapid at a rate of approximately 200. The rate slowed after a few seconds with a progressively diminishing number of extrasystoles. Following apnea the respirations would return, starting

with a few gasps. There would be a concomitant improvement in color, and the patient generally returned to consciousness, usually remarking about the severity of the attack. On a few occasions he remained disoriented for as long as one to two hours after the attack.

The third attack after admission was recorded completely by the electrocardiograph, and the oral administration of quinidine sulphate was then instituted. In the twenty-four hours before the medication was started, the patient had had seven syncopal attacks.

That evening he was given two doses of 0.3 gm. each of quinidine sulphate, the last at midnight. On the second day he was given 0.3 gm. at 10 A.M. and 0.5 gm. at 2 P.M. and 6 P.M. He had two short syncopal attacks that afternoon, but that night at 2:40 A.M. he had a severe attack from which he did not completely recover

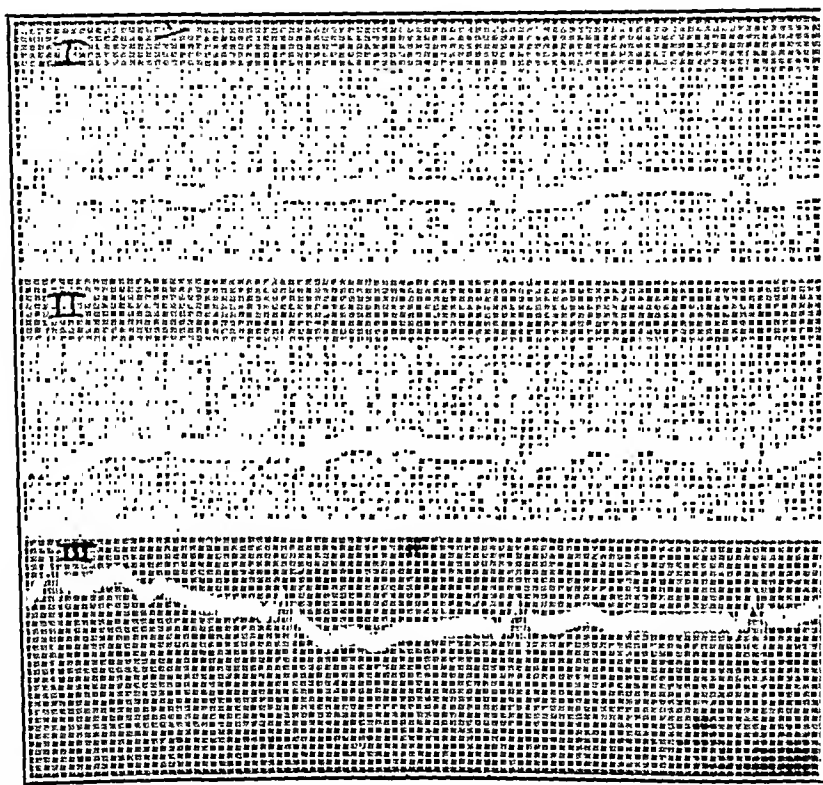


Fig. 5.—(Leads I, II and III) Taken during the second hospital admission when the patient was receiving large doses of quinidine (0.5 gm. 5 i.d.). Showing nodal rhythm.

for two hours. The heart rate did not return to normal, but frequent extrasystoles kept it irregular at a rate of 120 per minute, and the patient remained agitated and markedly disoriented for approximately one hour. He then partially recovered and was given 0.008 gm. of morphine sulphate hypodermically. This quieted him, and after another hour he returned to sleep.

It was then decided to decrease the time interval between the last dose of quinidine in the evening and the first dose in the morning, and on his third day the patient received 0.5 gm. of quinidine at 10 A.M. and 0.4 gm. at 2 P.M., 6 P.M. and 10 P.M. On the fourth day he was given 0.4 gm. five times, the first dose at 6 A.M. and the last at 10 P.M. There were no further syncopal attacks during the hospital stay, and on the sixth day reduction of the dosage was started. On the eighth day he was allowed out of bed, and by the tenth day he was receiving only 0.3 gm. of quinidine three times a day at 8 A.M., 2 P.M. and 8 P.M. On the fifteenth day this was reduced to 0.3 gm. twice a day at 8 A.M. and 8 P.M.

By the tenth day his white blood cell count had fallen to 6,550 per c. mm. and his urine had cleared completely. His temperature which was elevated to 99° F. in the afternoon during his first week in the hospital remained below 98.6° F. thereafter. The blood pressure showed a gradual elevation and on the fifteenth day was 174 mm. systolic and 88 mm. diastolic.

The patient was discharged from the hospital eighteen days after admission feeling quite well. He was advised to take 0.3 gm. of quinidine sulphate at 8 A.M. and 8 P.M. every day.

Interval history.—He returned five weeks after discharge to report that on a régime of limited activity he had had several bouts of "gas" and one attack of syncope. He had been taking his quinidine regularly. The bouts of "gas" were essentially the fullness in the epigastrium ascending to the neck as described before, associated with numbness in both arms and transient vertigo. The syncopal attack had occurred while he was asleep, and according to his family who were aroused by his stertorous breathing, it lasted only a few minutes. He felt perfectly normal after the attack. Physical examination at the time of the visit showed no change. The heart was slow and regular except for occasional extrasystoles. The blood pressure had risen to 200 mm. systolic and 96 mm. diastolic. Because of the syncopal attack he was advised to increase his daily dose of quinidine to 0.3 gm. three times a day to be taken at 8 A.M., 2 P.M. and 8 P.M. An electrocardiogram taken at that time showed nodal rhythm and left ventricular preponderance. The rate was 60.

His next visit was three weeks later (two months after discharge). He had had no further syncopal attacks. His heart rhythm was regular, rate 80.

He felt well until four and a half months after discharge when on November 23, 1932, he had a syncopal attack shortly after awakening. He remained in bed, but had three more during the day and was advised by his physician to reenter the hospital.

Summary of the Second Hospital Admission.—Physical examination was essentially as before with the blood pressure at 195 mm. systolic and 68 mm. diastolic. Examination of the heart showed frequent extrasystoles with occasional regular occurrence causing apparent coupling. Several short runs of eight to ten rapid beats were noted.

The quinidine dosage was increased gradually until on the fifth day he was receiving 0.5 gm. five times a day. At this point his attacks of syncope ceased. He had then had nine syncopal seizures in five days. Four days after his last attack he was allowed out of bed and the quinidine was discontinued. The lack of medication worried him so placebo pills were substituted. However, he had no more attacks and was discharged on the eighteenth day with instructions to resume quinidine 0.3 gm. at 7 A.M., 2 P.M. and 6 P.M.

A seven-foot roentgen-ray examination of the heart taken during this admission showed a definite increase in the heart size since the previous examination, more marked to the left. Measurements were: Midline to right border 5.2 cm., midline to left border 10.9 cm., great vessels 5.6 cm., internal diameter of the chest 29.0 cm.

Interval History.—The patient returned home and led a sedentary life, taking quinidine three times a day as instructed. On this régime he felt well except for occasional dizzy spells. However, two weeks after discharge he had a typical syncopal attack, and two days later had four more attacks, one of which was said by his family to be particularly severe. He voluntarily increased his quinidine to 0.3 gm. four times a day. The next morning, however, he had another syncopal seizure and finally was advised to reenter the hospital on Dec. 27, 1932, seventeen days after his previous discharge.

Summary of the Third Hospital Admission.—Physical examination was essentially as before. The blood pressure was 170 mm. systolic and 80 mm. diastolic. Regularly occurring extrasystoles caused a coupled heart rhythm.

On the afternoon of admission it was decided to try the effect of immediate withdrawal of the quinidine. At this point the patient had had six attacks in four days. Placebo medication was again substituted, but he had no further attacks, his heart remaining regular at approximately 50.

On the seventh day he was allowed out of bed, and as his activity increased, he again began to have extrasystoles. These gradually increased in frequency until on the fifteenth day periods of coupled rhythm were heard. On the sixteenth day he had another syncopal attack and was again kept in bed. The attacks ceased, but frequent extrasystoles were still heard.

On the seventeenth day quinidine sulphate was resumed. However, he again began to have attacks, and the dosage of quinidine was increased until on the twenty-third day he received 0.6 gm. four times. At this point the attacks again ceased, and as the patient was complaining considerably of vertigo and tinnitus, the dose was cut to 0.4 gm. four times a day where it was maintained. During the preceding seven days he had had eleven attacks.

He then had no further syncopal seizures, and on the twenty-sixth day was allowed out of bed. His heart remained perfectly regular on normal activity about the ward. Quinidine was again discontinued on the thirty-fifth day, no placebos being substituted at this time. That night, eight hours after his last dose of quinidine, he had a spell of transient vertigo, but thereafter his heart rhythm became perfectly regular and remained so through the forty-third day. The patient's general well-being seemed to increase and he felt quite normal.

During this admission he continued to run a slight elevation of temperature to between 99° and 100° F. with a leucocyte count that varied between 14,200 and 7,400 per c. mm. His urine showed a slight trace of albumin on entry, but then cleared completely and phenolsulphonephthalein excretion in the urine was 53 per cent in two hours and ten minutes after intramuscular injection.

DISCUSSION

From the observation of this case, no definite conclusion can be drawn regarding the value of quinidine sulphate in preventing ventricular fibrillation. During the first two admissions it seemed that the increased dosage of quinidine was responsible for the cessation of the syncopal attacks, but withdrawal of the quinidine shortly after entry on the third admission had the same result. A maintenance dose of quinidine kept the patient well for a time, but repeated syncopal attacks were liable to recur and similar periods of freedom from attacks were observed without medication.

The time relations between the attacks and the ingestion of the quinidine were noted on the second and third admissions. Several of the attacks were in the early morning before the first dose. During the second admission the shortest interval was two hours and thirty-five minutes after a dose of 0.3 gm., other short intervals being three and three and one-half hours after doses of 0.5 gm. One attack started five minutes after the drug was taken, but this interval was too short for the quinidine to have taken effect. During the third admission two syncopal attacks occurred one and one-half hours after doses of 0.5 gm. All medication was oral.

It seems logical to conclude that since quinidine prolongs the refractory period of the heart muscle, its use should help to prevent

ventricular fibrillation, as it apparently does ventricular tachycardia. However, Davis and Sprague³ and Davis⁶ believe that it is the normal conduction system that aids in preventing the onset of fibrillation and reason that, if the conduction fibers are already damaged, the toxic effect of the quinidine would further depress their function and outweigh the effect on the ventricular muscle. The drug would, therefore, allow fibrillation to start more easily. Schwartz⁷ and Schwartz and Jezer⁸ have recently reported several cases of paroxysmal ventricular fibrillation, all of which showed evidences of conduction system damage in the form of complete heart-block. They did not mention the use of quinidine in any of these cases.

The case here reported has shown no evidence of conduction system damage, so should have been an ideal one to demonstrate the value of the drug in preventing fibrillation by its action on the ventricular muscle. Although observation of the case over a period of seven months gives the impression that quinidine sulphate is of some benefit, it has been impossible to prove the fact conclusively.

SUMMARY

A case is reported which showed syncopal attacks proved by the electrocardiograph to be due to transient ventricular fibrillation. The attacks were usually preceded by increasing numbers of ventricular extrasystoles leading into short runs of ventricular tachycardia. Therapy with quinidine sulphate in varying doses was tried over a period of seven months with control periods during which the drug was withheld. During this time there were three hospital admissions. From these observations it seemed that quinidine was of some value, but the effect was not invariable enough to enable one to draw any absolute conclusions as to its efficacy.

I wish to thank Dr. S. A. Levine for his help and suggestions in the preparation of this case report.

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Department of Reviews and Abstracts

Selected Abstracts

Callow, Bessie R.: Bacteriologic Investigation of the Blood in Rheumatic Fever. *J. Infect. Dis.* 52: 279, 1933.

The original object of this investigation was to demonstrate the presence or the absence of microorganisms in the blood stream of patients with rheumatic fever. Cultures were made of the blood of 174 patients; 60 per cent of these were subject to blood culture from two to seven times, and a total of 367 cultures was examined. The blood was also studied in a series of patients who gave no history of rheumatic disease.

The frequent isolation of *Streptococcus viridans* and of pleomorphic bacilli from single and repeated blood cultures of patients with rheumatic fever in which the type of organism seemed to bear no relation to the stage or manifestation of the disease and a similar incidence of the same types of organisms in blood cultures of patients with nonrheumatic diseases who gave no history of rheumatic manifestations stimulated a study of the organisms from the point of view of their morphologic and cultural characteristics, biochemical reactions and serologic behavior.

The majority of the strains of *Streptococcus viridans* from blood cultures of rheumatic and nonrheumatic subjects were identified as lanceolate cocci and diplococci, all of which had similar cultural characteristics. A large proportion of the strains tested (63 per cent) fermented mannite and belonged mostly in the *Streptococcus faecalis* group. Other strains from the two sources were grouped with *Streptococcus salivarius* and *Streptococcus mitis*. The application of the bile-heat-esculin test further correlated all diplococcic strains fermenting mannite, whether of rheumatic or nonrheumatic origin, with members of the enterococcus group.

Strains of pleomorphic bacilli from blood cultures of rheumatic and nonrheumatic subjects were similar morphologically, culturally and biochemically.

The bacillary and streptococcic strains varied not only in morphologic and cultural characteristics, effect on red blood cells and serologic reactions, but also in metabolism. The bacillary strains are obligate aerobes, are biologically inactive to sugars and form catalase. The streptococcic strains are facultative anaerobes, are biologically active to sugars, and produce dioxide.

Six experiments are presented which illustrate that under controlled conditions selected strains of pleomorphic bacilli were transformed into diplostreptococci of the green and hemolytic types. The coccic derivatives were similar in all respects to the diplococci originally isolated from the blood cultures of rheumatic and non-rheumatic subjects.

A definite antigenic relationship was established between selected strains of pleomorphic bacilli and their coccic derivatives, also related coccic organisms (both original and derived) by means of reciprocal agglutination and absorption tests. These principles were applied to the study of pleomorphic bacilli and streptococci from repeated blood cultures of the same patient.

Reciprocal agglutination and absorption tests also identified strains of pleomorphic bacilli from repeated blood cultures of several patients and were used in the identification of the coccic derivatives of selected bacillary strains.

It was possible to group 21 streptococcic strains (including 2 strains from patients with subacute bacterial endocarditis and some coccic derivatives) from blood cultures of rheumatic and nonrheumatic subjects into one major group and four subgroups by means of the reciprocal tests. A large series of additional strains from these sources also showed some relationship to the ones in the groups defined. The disease in question, however, whether rheumatic or nonrheumatic, did not appear to be a determining factor in the relationships disclosed.

With one exception, it was not possible to demonstrate agglutinins for the homologous organisms in the serum of patients with rheumatic fever taken at frequent intervals during the course of the disease.

From these studies the author concludes that diplostreptococci (alpha type) and pleomorphic bacilli may be recovered repeatedly from the blood of patients with rheumatic fever and certain diseases mostly of the upper respiratory tract. These organisms apparently represent stages in the life cycle of the same organism. A specific etiologic relationship between these organisms and rheumatic fever is questioned.

Hitchcock, Charles H., and Swift, Homer F.: The Agglutinating Properties of Exudates From Patients With Rheumatic Fever. *J. Clin. Investigation* 12: 673, 1933.

During the course of a search for agglutinins and precipitins in the body fluids of patients suffering from various acute manifestations of rheumatic fever, it was observed that exudate obtained from the knee during the course of an acute arthritis possessed a marked capacity to cause flocculent growth (thread reaction) of a certain strain of *Streptococcus hemolyticus*. This strain had been kept in the laboratory for many years on artificial media. So striking was this effect noted at times in a dilution of 1:10,000 of the exudate that it seemed desirable to extend the observation to other organisms, as well as to include exudates from conditions other than rheumatic fever.

Joint, pleural and pericardial exudates from patients with rheumatic fever caused clumped growth of certain strains of hemolytic streptococci and staphylococci when tested by the thread reaction. Certain other varieties of bacteria are unaffected. This property is possessed in lesser degree by exudates from non-rheumatic patients.

It was found that old laboratory strains are suitable for demonstration of the reaction, while freshly isolated strains are usually unsuitable. The active material is greatly reduced in potency by heating at 56° C. It is not reactivated by the addition of complement.

It is concluded that these observations have no necessary bearing upon the question of the etiology of rheumatic fever.

Benson, Robert L., Hunter, Warren C., and Manlove, Charles H.: Spontaneous Rupture of the Heart. Report of 40 Cases in Portland, Oregon. *Am. J. Path.* 9: 295, 1933.

Forty ruptures of the heart have been collected from nearly 7,000 autopsies in Portland, Oregon. One of these was probably of syphilitic origin; another, a dissecting aneurysm of a sinus of Valsalva, was due to *Streptococcus viridans* endocarditis. The remaining 38 ruptures, although in some instances manifesting evidence of syphilis, were attributable to recent or old thrombosis, embolism or

arteriosclerosis of the coronary arteries. The cases are analyzed in detail and classified in groups. They have been studied particularly from the standpoint of location of the rupture. It was noted that in this group cholelithiasis was coincidentally present in 17.5 per cent of the cases.

Herrmann, George, Schwab, E. H., Stone, C. T., and Marr, W. L.: On the Advantage of Alternating the Vegetable and Metallic Diuretics in the Treatment of Edema of Congestive Heart Failure. *J. Lab. & Clin. M.* 18: 902, 1933.

Clinical evidence seems to substantiate the idea that purine diuretics act primarily by increasing the glomerular filtration rate, while the heavy metals accomplish their results principally by decreasing the tubular reabsorption. Advantage was taken of these hypothetical considerations of the two different modes of action of the two diuretic drugs in the hope of getting better results by rational combination régimes. Distinctly practical advances in the treatment of the vicious circle of edema in congestive heart failure are demonstrated by the study. The purines and heavy metal diuretics can be so combined (1) as to produce diuresis when either one of the drugs used alone in maximum dose has been ineffectual, (2) as to accomplish the greatest possible diuresis in the shortest interval of time, (3) as to obtain a perfectly satisfactory diuresis by smaller and absolutely harmless doses which alone would prove inadequate.

Zierold, Arthur A.: The Surgical Treatment of Arterial Embolism. *J. A. M. A.* 101: 7, 1933.

The author reports a series of 20 cases of auricular embolism in 11 of which surgical treatment was undertaken. The operation consisted of the exposure of the affected vessel at the site of obstruction and the removal of the obstructing embolus and thrombus by arteriotomy. In one case the femoral vein was ligated and the artery was not opened. A discussion of the physical signs by which the cases may be selected for operation together with important secondary procedures in the treatment of these cases is presented.

In view of the fact that arterial emboli are not uncommon phenomena, especially in association with heart disease, this principle of treatment should receive active consideration from physicians. If the location of the embolus can be identified and is in some accessible part, such an operation should be contemplated. The author believes there is no simple operation in surgery so eminently satisfactory or attended by great potentiality for good as arteriotomy for arterial embolism.

Bass, Murray H., Mond, Herman, Messeloff, Charles R., and Oppenheimer, Enid T.: Systolic Murmurs in Children. *J. A. M. A.* 101: 17, 1933.

Sixty-four children with systolic murmurs, both organic and functional were studied clinically and phonocardiographically; the records of all the murmurs contained vibrations of high frequency. Eighty-six per cent of the functional cases presented high-pitched vibrations only, while organic cases revealed low as well as high-pitched vibrations. This suggests an additional means of differentiating between the two types of murmurs.

Irvine-Jones, Edith: Acute Rheumatism as a Familial Disease. *A. J. Dis Child.* 45: 1184, 1933.

This study of rheumatism was undertaken to show the relative importance of heredity in constitution contrasted with infectivity as factors in the occurrence of the disease. Five hundred families with rheumatic members were investigated

in St. Louis and Toronto, Canada. These families represented more than 800 rheumatic subjects.

From the study, the impression is confirmed that rheumatism tends to attack more than one member in a family. It has been shown that the incidence in multiple cases in families was about equal in Toronto and St. Louis but that the number infected per family was higher and the age of onset lower in Toronto. Simultaneous attacks were shown to be frequent. It has been shown also that rheumatism is more common in the more distant relatives of rheumatic families than in those of controls. It affected both of two pairs of identical twins simultaneously but only one set of each pair of the dissimilar twins. This condition was also commoner in the families in which the father was affected, which would surely not be the case if contagion were the prime factor. Rheumatism tended to occur in blond and red-haired persons, particularly in those with bluish yellow or hazel eyes, but these characteristics were also found in the nonrheumatic relatives of those persons. The coloring thus had no bearing on the actual occurrence of rheumatism but pointed to a type in which rheumatism frequently occurs.

The author believes from the foregoing evidence that undoubted familial occurrence of rheumatism would seem to be due less to a specific and contagious agent than to certain familial characteristics which favor: (a) the onset of many infections and (b) the appearance of the syndrome known as rheumatism. The determining factor in rheumatism may be nonspecific, since other acute infections of a different nature may arise simultaneously with rheumatic manifestations. Simultaneous attacks of rheumatism would then be explained by some nonspecific but infective agent attacking several people of like "rheumatic" constitution. This is in keeping with the growing opinion of bacteriologists that rheumatism is a specialized type of reaction to a common infective agent.

Wilson, May G., and Edmond, Helen: Blood Cultures in Children With Rheumatic Fever. *A. J. Dis. Child.* 45: 1237, 1933.

A total of 236 blood cultures from 67 children with rheumatic disease was studied. In 46 per cent of these children positive cultures were secured. The positive cultures were obtained in 37 per cent during the active stage and in 41 per cent during the apparently inactive period. In a control series which included normal infants and children as well as those who were ill or convalescing from various infections, 153 blood cultures from 78 children and 13 adults were studied. Forty-one per cent of these cultures were positive. The positive cultures were secured in 33 per cent of the healthy infants and children of this control group.

The microorganisms recovered from all the blood cultures were of three types: *Streptococcus viridans*, *Streptococcus anhemolyticus* and pleomorphic bacilli. About one-half of the organisms recovered were streptococci; the rest were pleomorphic bacilli. The incubation period varied from three to thirty-two days. About one-half of the strains were recovered within a two weeks' period of incubation.

It is concluded from this study that organisms may be recovered from the blood cultures of healthy infants and children and from children acutely ill or convalescing from various infections with this bacteriological method. In view of the results obtained in the control series, the presence of these organisms in the blood cultures of children with rheumatic disease would not appear to be of primary etiological significance. The incidence of recovery of organisms from both the rheumatic and the control series was comparable.

Coombs, Carey F.: Thirty Years' Progress in the Study of Rheumatic Heart Disease. *Bristol Med-Chirur. J.* 50: 93, 1933.

This lecture prepared by Dr. Coombs before his death is printed as it was delivered. In it he reviews in interesting and pleasing style the progress that has

been made in our knowledge of this disease. He discusses the early ideas that prevailed among the workers in the English schools at the time the author came under the influence of Dr. Cheadle. He also discusses the present conception of the disease, outlining briefly the various factors that contribute to its incidence.

The main interest in the article centers in the fact that it represents the reflections of one who himself contributed a great deal to the subject and who was constantly in contact with other workers who have played important parts in advancing our knowledge of this condition.

Bohning, Anne, and Katz, Louis N.: Unusual Changes in the Electrocardiograms of Patients With Recent Coronary Occlusion. A. J. M. Sc. 186: 39, 1933.

Electrocardiograms are presented of ten patients having a clinical history typical of protracted or transient coronary occlusion of recent origin.

The most significant findings in cases of recent coronary occlusion are changes in the form of the S-T segment and the T-wave; either an elevation, a depression or an inversion. The most significant fact is that a definite change is present, whether it be in an upward or in a downward direction. Successive records usually show a rapid change in contour in the early stages of coronary occlusion. Not all curves in recent coronary cases can be fitted into the T_1 and T_2 types of Parkinson and Bedford.

Attention is drawn to a large, upright, sharply peaked T wave whose limbs and shoulders are symmetrical and have their convexity pointing downward and toward each other, associated with an isoelectric or negative S-T interval having a "hump" pointing down. It is different from the nonspecific, tall T-wave. This large upright T-wave is most commonly found in Leads II and III of the T_1 type and is as diagnostic a feature of the coronary occlusion type of curve as the inverted cove-shaped T-wave of which it is the inverse image. The authors have designated this characteristic as the upright coronary T-wave.

Edeiken, Joseph: The Effect of Spinal Deformities on the Heart. A. J. M. Sc. 186: 99, 1933.

Spinal deformities, especially scoliosis and kyphoscoliosis have a profound effect upon the lungs, and the effect upon the heart is probably secondary to the latter in most cases. Kinking or twisting of the great vessels as the result of displacement of the heart may be responsible for certain cardiac signs and symptoms.

Most patients with kyphoscoliosis and severe grades of scoliosis have signs of right-sided disturbance of cardiac function. However, they may live for years, many being restricted in activity because of dyspnea on exertion. Some are cyanotic and a few show edema of the legs. According to the literature most patients die of a pulmonary complication.

Kyphoscoliosis causes marked changes in the size, shape and position of the heart. The shape and position of the heart vary considerably from case to case.

The aorta tends to follow the spine in spite of the deformity. In two cases of right kyphoscoliosis observed postmortem, the aorta coursed directly across the thorax to reach the spine.

Pure scoliosis due to organic disease is relatively uncommon and is usually right-sided. In the latter, the heart is displaced and often rotated to the left, causing it to appear "mitralized." The aortic knob appears very sharp in some cases. Left scoliosis causes the heart to become centrally placed and the aortic area to appear widened. The aortic diameter, however, is not increased.

Three of the four cases of kyphosis included in this study presented cardiac complaints but there were complicating factors in each case sufficient to account for the symptoms. In pure kyphosis the anteroposterior transverse diameter ratio tends to be greater than normal.

Two cases of lordosis presented no cardiac symptoms. The anteroposterior transverse diameter ratio was smaller than normal in both.

Except for axis deviation in six instances, the electrocardiogram was normal in 20 of 24 cases of spinal deformity. Two of the four abnormal electrocardiograms were in patients with hyperthyroidism and hypertension. The infrequency of axis deviation despite displacement and rotation of the heart is probably due to the opposing effects of rotation around longitudinal and anteroposterior axes.

Nylin, Gustav: *Clinical Tests of the Function of the Heart.* Acta Medica Scandinavica, Supplement 52, 1933.

The object of this investigation was to determine before and at fixed times after graduated work, the oxygen consumption, minute volume of the heart, blood pressure and pulse rate, according to a preliminary report.

The increase in oxygen consumption as a percentage of the resting value after a fixed amount of work on the stairs varies within fairly narrow limits in healthy individuals and is independent of body weight, provided that the latter is within physiological limits.

In decompensated heart disease patients and cases of decompensated hypertonia, this increase is consistently greater than in the healthy cases, so that it seems to be a reliable measure of pronounced heart insufficiency, though this is more doubtful with borderline cases. At the same time as the insufficiency yields to treatment, a reduction of the oxygen consumption after work often sets in.

In spite of the paucity of the material, the author believes that the function test according to this method is of practical value in judging as to the presence or otherwise of heart insufficiency, especially in cases of heart neurosis, hypertonia and obesity.

The increase in ventilation after work is a far less reliable measure of the decompensation than the increase in oxygen consumption.

The pulse rate, utilization and standard metabolism, are increased in many decompensated heart disease and hypertonia cases during rest, but, on the other hand, the minute volume, the minute volume/m² body surface, and the systolic output, are reduced. Determinations of these functions of the circulation cannot be used, however, as a method of functional heart diagnosis, as the values for healthy and decompensated cases partly overlap.

The systolic output/m² body surface in the decompensated cases appears to be considerably reduced, so that its determination is of greater importance than that of the functions mentioned in paragraph 4.

The utilization, i.e., the oxygen absorption per liter of blood, after a fixed amount of work, returns more quickly to the resting value in healthy persons than in severe decompensation cases.

The return of the systolic blood pressure and pulse rate to the resting value, after a fixed amount of work, is slower in decompensation cases than in healthy persons. Owing to the fact that the distribution of the values for healthy persons and decompensation cases partly overlaps, determinations of these functions severally cannot be used as measures of heart insufficiency.

The return of the Liljestrand-Zander's product is retarded in the decompensated cases.

Hinrichsen, Josephine, and Ivy, A. C.: *Effect of Stimulation of Visceral Nerves on Coronary Flow in Dogs.* Arch. Int. Med. 51: 932, 1933.

The usual result of stimulating the central end of sensory nerves innervating the upper abdominal viscera or of distending the viscera on coronary flow is an increase in flow. An unquestionable decrease in flow occurred in only two of forty-nine tests, whereas an unquestionable increase in flow occurred in nineteen of thirty-nine tests. In the dog, reflex coronary dilatation is more readily demonstrated than reflex constriction.

The authors are inclined to accept the view of Greene, who has performed similar experiments on the dog, namely, that the failure of the reflex coronary dilator mechanism most likely accounts for the association of angina pectoris with visceral distention or excitation.

Blumgart, Herrman L., Levine, Samuel A., and Berlin, David D.: *Congestive Heart Failure and Angina Pectoris. The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity.* Arch. Int. Med. 51: 866, 1933.

Reasons are given for believing that patients with a normal metabolism who suffer from congestive heart failure or angina pectoris might show striking improvement if the metabolic rate were significantly lowered. The hearts of such people might be unable to supply enough blood for the ordinary demands of a normal metabolic rate but, nevertheless, might be able to supply enough blood for a reduced metabolic rate. The present communication reports the results of producing a subnormal metabolic rate by thyroidectomy on three patients who were suffering from severe congestive heart failure but who showed no evidences of disturbed thyroid function and on one patient with angina pectoris with a slight elevation of metabolism but with a normal gland. In the patients studied the signs and symptoms of circulatory insufficiency and of angina pectoris had persisted for a considerable time in spite of all known medical procedures. The clinical condition of each patient was accurately studied during a long control period in order that any change following thyroidectomy could be attributed confidently to the effect of the procedure.

In two of the three patients with severe congestive heart failure subtotal thyroidectomy caused a fall in the metabolic rate which reached its maximum about three weeks after operation. Clinical improvement paralleled the lowered metabolism and was evidenced by the disappearance of edema, the increased vital capacity of the lungs and the ability to be up and about the ward with comfort. During the next few weeks, the basal metabolic rates in these two patients again rose toward the preoperative normal level and their clinical conditions became less favorable. One of these patients continued for an additional month to show a somewhat lessened metabolic rate than before operation, and his clinical condition, while not so good as that three weeks following operation, was definitely better than before operation. The patient with angina pectoris has shown no recurrence of the attacks of angina pectoris since subtotal thyroidectomy, although he has returned to work and active life. This is in contrast to his condition before operation, when attacks of angina pectoris occurred even while he was at rest.

In one patient with congestive heart failure complete ablation of all thyroid tissue was done, the parathyroid glands being spared. This patient has maintained his conspicuous clinical improvement, and the metabolic rate has remained persistently lowered for more than six weeks. Further studies are being made in order to appraise the value of thyroidectomy and the effect of roentgen irradiation.

tion more accurately. The application of this procedure to other conditions in which a lowering of the metabolic rate may prove beneficial is also being studied. In the meantime, the procedure should be employed only in carefully selected cases in which all known therapeutic measures have proved ineffectual.

Parsonnet, Aaron E., and Parent, Sol: Auricular Flutter With Complete Auriculo-Ventricular Block in a Patient With Coronary Disease. *Arch. Int. Med.* 51: 938, 1933.

A case of auricular flutter with an unusually high auricular rate is reported. This condition was superimposed over a complete dissociation of the auricles and ventricles in a patient who subsequently died with all the classic manifestations of coronary occlusion and infarction. The rarity of such a combination of abnormal rhythms, the extremely high auricular rate, the rapid changes of axis in the various leads, the clear demonstration of flutter configuration in Lead I and finally, the typical T-waves as seen in coronary disturbances are of singular interest.

Hoffman, Arthur M., and Delong, Everett: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage. *Arch. Int. Med.* 51: 947, 1933.

A standard technic for obtaining chest leads is presented.

The position of the electrode on the chest is of importance. Uniform tracings can be secured in normal patients by this technic. In diseased hearts, two positions may show abnormal chest leads. Usually, however, only one of these positions shows such an abnormality. When present in both positions, one may revert to normal earlier than the other.

The changes found are not specific for coronary thrombosis, for they were found in other types of myocardial damage confirmed by autopsy. In patients with coronary thrombosis, however, a relatively characteristic chest lead deformity is noticed. Besides Wolferth and Wood's S. T. deformity, the authors found a more frequent abnormality of an isoelectric or upright T-wave in Lead IV. These T-wave abnormalities in the chest lead occasionally precede changes in the standard leads and are, therefore, of value in an earlier confirmation of a diagnosis of coronary thrombosis. They also occur in instances in which the standard leads show the characteristic abnormalities of coronary thrombosis. In some cases of this type, the Lead IV changes may be absent. The chest lead abnormalities change with improvement in the patient's condition, implying that an acute underlying process is taking place. Occasionally a return to normal occurs in the chest lead but not in the standard leads. The reverse of this appears to occur even more frequently.

As pathological changes which occur in the myocardium are not all recorded in either the chest leads or the routine leads alone, the authors feel that it is a worth-while procedure to run the chest leads in all cases of suspected or proved myocardial damage. In all the patients on whom such tracings were taken, in whom there was clinical evidence of heart disease, either the chest lead or the routine leads showed evidence of myocardial damage. In none of these patients were both the routine and the chest leads found to be normal.

Rosenblum, Harold H., and Levine, Samuel A.: What Happens Eventually to Patients With Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? *Am. J. M. Sc.* 185: 219, 1933.

A follow-up study was made of 69 "thyrocardiacs" in whom subtotal thyroidectomy was performed. All of these patients before operation had gross evidence of congestive

or anginal heart failure. There were 2 postoperative fatalities, and of the remainder the average length of follow-up was four to five years. Six patients died since the operation after an average survival of 2.5 years. These 6 had been restored either to normal health or to resumption of moderate activities.

Forty-three patients had objective evidence of congestive heart failure; 9 had angina pectoris, 2 of whom had had coronary thrombosis; 15 had definite mitral stenosis and 4 had questionable mitral stenosis; 2 had aortic insufficiency (1 was luetic, 1 rheumatic); 35 patients had hypertensive heart disease.

The average basal metabolic rate before operation was +51.1 and +4.8 per cent after operation. The average preoperative blood pressure was 153 mm. systolic and 81 mm. diastolic. The heart size was practically unchanged as a result of operation. The average preoperative transverse diameter of the heart in 10 patients was 14.3 cm., and postoperatively it was 14.2 cm. All but 7 of the 69 showed some type of heart murmur before operation.

In 27 patients specific notation was made concerning the presence of murmurs before and after operation. All these patients had systolic murmurs and 8 had diastolic murmurs. In 16 instances a preoperative systolic murmur disappeared, in 8 it became less marked, and in 3 it remained unchanged. Of the 8 diastolic murmurs, 6 were due to mitral stenosis and 2 to aortic insufficiency. Three of the former and 1 of the latter first became audible postoperatively.

Of 32 patients who had established auricular fibrillation, 24 were adequately re-examined. Of these 11 had mitral stenosis, and in none of these did the auricular fibrillation spontaneously disappear. Of the remaining 13, 6 reverted to normal rhythm after operation and the cardiac rhythm remained regular for years. There were an additional 11 patients who showed paroxysmal auricular fibrillation. In practically all instances these paroxysms did not recur after the patients left the hospital.

Our experience with quinidin in these cases indicates that it is useless to employ it preoperatively for auricular fibrillation and dangerous to give it postoperatively to those patients with mitral stenosis and auricular fibrillation. It is best given a few weeks after operation to those without mitral stenosis in whom auricular fibrillation is still persisting.

Six cases of paroxysmal auricular flutter occurred in this series. These attacks disappeared permanently in all but 1 of the cases. In the latter instance there was a single return of this arrhythmia associated with some evidence of persisting hyperthyroidism.

Sinus pauses occurred in 2 patients who were both permanently relieved following operation. There were 2 instances of delayed auriculoventricular conduction, 1 of which became normal after subtotal thyroidectomy.

Extrasystoles were relatively uncommon; there were only 6 instances of this irregularity in the group studied.

The great rarity of congestive heart failure in young patients with hyperthyroidism and the almost uniformity of other forms of heart disease (mitral stenosis, hypertension, coronary artery disease, etc.) in those with significant cardiac embarrassment make it probable that hyperthyroidism is rarely the sole cause of heart failure.

The follow-up study of these cases showed that not only was there marked immediate improvement following operation in the various evidences of circulatory embarrassment, such as congestive heart failure, angina pectoris and disturbing irregularities of the heart, but the improvement was extremely well maintained.

The occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive heart failure, in whom the thyroid gland was normal, suggests that this operation may be useful more generally in the treatment of various forms of cardiac disease.

Book Reviews

KREISLAUFSTÖRUNGEN UND PATHOLOGISCHE HISTOLOGIE. By Prof. Dr. Martin Nordmann, Privatdozent, University of Tübingen. (Ergebnisse der Kreislaufforschung, Band iv.) 174 pp. Dresden and Leipzig, 1933, Theodor Steinkopff.

This is a review of the literature (for the most part German) dealing with the more manifest disturbances of the circulation in the peripheral vessels, from the clinical as well as the pathological-histological standpoint. It stresses the desirability of many modes of approach to the subject with an attempt at correlation. The author deplores the lack of attention to Roekitansky's point of view. He states that Thoma is the only one who holds with him that phenomena consequent upon circulatory disturbances include all conditions of pathological anatomy. It is an interesting account of the German contributions to the subject of vascular disease.

A. R. B.

DIE BRUSTWANDPULSATIONEN ALS SYMPTOME VON HERZ- UND GEFÄSSKRANKHEITEN. By Dr. Wilhelm Dressler, Assistant in the Heart Station in Vienna. 181 pp., with 87 illustrations. Vienna, 1933, Wilhelm Mandrich.

Dr. Dressler's careful clinical study of pulsations of the chest wall is a notable example of work based on the skillful use of the senses as opposed to a study requiring complicated apparatus. Dr. Dressler reviews the important anatomical and physiological relationships and shows how these affect the pulsations which may be seen or felt in health and in disease. The first part of the book is given over to general considerations; the second to a discussion of the modification of the pulsations under special conditions. The style is clear and the method of presentation interesting. Dr. Dressler has used graphic methods for control purposes, but he has wisely chosen to present his material as a study in physical diagnosis and clinical observation, and as such it should be of special interest to teachers and clinicians.

E. H.

CARDIOVASCULAR PAIN AS A BIOCHEMICAL PROBLEM. By Gordon Lambert, B. A., M.D., B.C. (Cantab.) 75 pages, with 23 illustrations. London, 1933, H. K. Lewis & Co., Ltd.

Contrary to the implication contained in its title, this little monograph proceeds to concern itself with a discussion of the "vascular, muscular and neural factors in cardiovascular pain." There are no original observations. The author has collected seventy-five references, many of them irrelevant. There are frequent quotations, but the recent work of Sir Thomas Lewis is not mentioned. The illustrations consist of crude pen and ink drawings; even the electrocardiograms appear as free-hand sketches.

After sixty-nine pages of futile argument, it is concluded that "biochemical research gives promise of adding to our knowledge, and further compilation of statistics, based solely upon morbid anatomy, cannot yield the same results."

In the opinion of this reviewer, the booklet serves no useful purpose. It neither contributes to our knowledge of cardiovascular pain, nor does it summarize in an adequate manner those facts which are known concerning it.

R. L. L.

Letter to Editor—Correction

Albany, N. Y.,

June 30, 1933.

Through a very regrettable oversight on my part a gross error appeared in my paper "Heart Disease in General Medical Practice," which was published in the April, 1933, issue of the Journal.

On page 7 the statement is made that "from four to eight million people in this country . . . suffer from heart disease." These figures, which are supposed to represent from two to four per cent of the population, clearly should read "from two and one-half to five million."

I shall be grateful to you if you will publish this correction in an early issue of the Journal.

Sincerely yours,

(Signed) J. V. DEPORTE,

Director, Division of Vital Statistics.

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